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Evaluation Report

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Sedaxane

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Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6604-E2
Ottawa, Ontario K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

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Table of Contents

Overview 1
  Registration Decision for Sedaxane 1
  What Does Health Canada Consider When Making a Registration Decision? 1
  What Is Sedaxane? 2
  Health Considerations 2
  Environmental Considerations 4
  Value Considerations 5
  Measures to Minimize Risk 5
  What Additional Scientific Information Is Being Requested? 6
  Other Information 6
Science Evaluation 7
1.0 The Active Ingredient, Its Properties and Uses 7
  1.1 Identity of the Active Ingredient 7
  1.2 Physical and Chemical Properties of the Active Ingredient and End-use Product 8
  1.3 Directions for Use 10
  1.4 Mode of Action 10
2.0 Methods of Analysis 10
  2.1 Methods for Analysis of the Active Ingredient 10
  2.2 Method for Formulation Analysis 11
  2.3 Methods for Residue Analysis 11
3.0 Impact on Human and Animal Health 12
  3.1 Toxicology Summary 12
    3.1.1 *Pest Control Products Act* Hazard Characterization 16
  3.2 Acute Reference Dose (ARfD) 17
  3.3 Acceptable Daily Intake (ADI) 17
  3.4 Occupational and Residential Risk Assessment 18
    3.4.1 Toxicological Endpoints 18
    3.4.2 Toxicological Endpoints 19
    3.4.3 Occupational Exposure and Risk 20
    3.4.4 Bystander Exposure and Risk 29
  3.5 Food Residues Exposure Assessment 29
    3.5.1 Residues in Plant and Animal Foodstuffs 29
    3.5.2 Dietary Risk Assessment 30
    3.5.3 Aggregate Exposure and Risk 31
    3.5.4 Maximum Residue Limits 31
4.0 Impact on the Environment 31
  4.1 Fate and Behaviour in the Environment 31
  4.2 Environmental Risk Characterization 32
    4.2.1 Risks to Terrestrial Organisms 33
    4.2.2 Risks to Aquatic Organisms 34

5.0 Value ... 37
5.1 Effectiveness Against Pests ... 37
5.2 Phytotoxicity ... 39
5.3 Economics ... 39
5.4 Sustainability ... 39
5.4.1 Survey of Alternatives ... 39
5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management ... 40
5.4.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance ... 40
5.4.4 Contribution to Risk Reduction and Sustainability ... 40
6.0 Pest Control Product Policy Considerations ... 40
6.1 Toxic Substances Management Policy Considerations ... 40
6.2 Formulants and Contaminants of Health or Environmental Concern ... 41
7.0 Summary ... 41
7.1 Human Health and Safety ... 41
7.2 Environmental Risk ... 42
7.3 Value ... 43
8.0 Regulatory Decision ... 43
List of Abbreviations ... 45
Appendix I Tables and Figures ... 49
Table 1 Residue Analysis ... 49
Table 2 Toxicity Profile of End-use Product(s) Containing Sedaxane ... 51
Table 3 Toxicity Profile of Technical Sedaxane ... 54
Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Sedaxane ... 62
Table 5 Integrated Food Residue Chemistry Summary ... 63
Table 6 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment ... 88
Table 7 Major Transformation Products in Environmental Media ... 89
Table 9 Risks to Terrestrial Organisms (Screening Level Assessment) ... 93
Table 10 Risk to Birds and Mammals (Screening Level Assessment) ... 94
Table 11 Risks to Aquatic Organisms (Screening Level Assessment) ... 95
Table 12 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria ... 96
Table 13 Fungicidal active ingredients in alternative seed treatments registered for crop diseases on the Sedaxane 500FS Fungicide, A17511B Seed Treatment and A16874F Seed Treatment Labels ... 97
Table 14 Use (label) claims for A16874F Seed Treatment and A17511B Seed Treatment proposed by applicant and whether acceptable or unsupported ... 100
Table 15 Sedaxane 500FS Fungicide use (label) claims proposed by applicant and whether acceptable or unsupported ... 101
Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications ... 103
Table 1 Comparison of Canadian MRLs, American Tolerances and Codex MRLs (where different) ... 103
References ... 105

Overview

Registration Decision for Sedaxane

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of Sedaxane Technical and A17511B Seed Treatment, containing sedaxane, difenconazole, metalaxyl-m and thiamethoxam, A16874F Seed Treatment, containing sedaxane, difenconazole and metalaxyl-m, and Sedaxane 500FS Fungicide, containing the technical grade active ingredient sedaxane, for use on seed from various crops including certain cereals (barley, wheat, oats, rye, and triticale), canola, and soybean to control or suppress soil and seed-borne diseases of seedlings and mature plants. A17511B Seed Treatment also contains an insecticide to suppress/control wireworm activity on certain cereal crops.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk reduction measures are followed, the applicant must submit additional scientific information as a condition of registration.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Sedaxane Technical, A17511B Seed Treatment, A16874F Seed Treatment and Sedaxane 500FS Fungicide.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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[1] "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

[2] "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment (for example most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What Is Sedaxane?

Sedaxane is the active ingredient present in three new seed treatment products: Sedaxane 500FS Fungicide (containing sedaxane), A17511B Seed Treatment (containing sedaxane, difenoconazole, metalaxyl-m, thiamethoxam) and A16874F Seed Treatment (containing sedaxane, difenoconazole, metalaxyl-m). Sedaxane is a preventative seed treatment with systemic properties that inhibits the normal respiration process in target pathogenic fungi. The new sedaxane-based products are intended for use on seed from various crops including certain cereals (barley, wheat, oats, rye, and triticale), canola, and soybean to control or suppress soil and seed-borne diseases of seedlings and mature plants. A17511B Seed Treatment also contains an insecticide (thiamethoxam) to suppress/control wireworm activity on certain cereal crops.

Health Considerations

Can Approved Uses of Sedaxane Affect Human Health?

Products containing sedaxane are unlikely to affect your health when used according to label directions.

Potential exposure to sedaxane may occur through the diet (food and water), when handling and applying the product or when entering treated sites. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, the active ingredient sedaxane and its associated end-use products, A17511B Seed Treatment, A16874F Seed Treatment and Sedaxane 500FS Fungicide, were of low acute toxicity by the oral, dermal and inhalation routes of exposure. They were minimally irritating to the eyes and non-irritating to the skin, and did not cause allergic skin reactions. Consequently, no hazard signal words are required on the labels.

Health effects in animals given repeated doses of the active ingredient sedaxane included effects on the liver, endocrine organs and circulatory system. Sedaxane did not cause birth defects in animals. When sedaxane was given to pregnant or nursing animals, effects on the developing fetus (a slight increase in abortions) and juvenile animal (decreased spleen weight) were observed at doses that were toxic to the mother, indicating that the young do not appear to be more sensitive to sedaxane than the adult animal. Sedaxane caused functional effects, possibly related to the nervous system, at high doses in rats. There was no evidence that sedaxane damaged genetic material but it did, however, cause liver tumours in mice and liver, thyroid and uterine tumours in rats. A cancer risk assessment was conducted based on the uterine tumours found in rats as this was protective of the other tumour types.

The risk assessment protects against the effects of sedaxane by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Aggregate dietary intake estimates (food plus water) revealed that the general population and infants, the subpopulation which would ingest the most sedaxane relative to body weight, are expected to be exposed to less than 0.9% of the acceptable daily intake. Based on these estimates, the chronic dietary risk from sedaxane is not of concern for all population sub-groups. The lifetime cancer risk from the use of sedaxane is considered acceptable (5.9×10^{-7}).

The acute aggregate (food and water) dietary intake estimate for each population subgroup ranged from 0.06% to 0.37% of the reference dose, which is not a health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted in the United States and Canada using sedaxane on barley, canola, soybean and wheat were acceptable. The MRLs for this active ingredient can be found in the Science Evaluation section of this Evaluation Document and in the Evaluation Reports under Application Numbers 2010-1525, 2010-1526, 2010-1527 and 2010-1529.

Occupational Risks From Handling Sedaxane 500FS Fungicide, A17511B Seed Treatment and A16874F Seed Treatment

Occupational risks are not of concern when Sedaxane 500FS Fungicide, A17511B Seed Treatment and A16874F Seed Treatment are used according to the proposed label directions, which include protective measures.

Workers treating seed with Sedaxane 500FS Fungicide, A17511B Seed Treatment or A16874F Seed Treatment in commercial seed treatment facilities, workers treating seed on-farm and workers planting treated seed can come into direct contact with sedaxane residues on the skin. Therefore, the label specifies that workers treating and handling treated seed must wear the following personal protective equipment (PPE). In commercial seed treatment facilities, workers treating, bagging, sewing, stacking, and forklifting treated seed must wear cotton coveralls over a long-sleeved shirt and long pants and chemical-resistant gloves. In addition, workers cleaning treatment equipment in commercial seed treatment facilities must wear chemical-resistant coveralls over a long-sleeved shirt and long pants and chemical-resistant gloves. Workers treating on-farm and/or planting treated seed must wear a long-sleeved shirt, long pants and chemical-resistant gloves. For good hygiene purposes, it is also recommended for workers to wear a NIOSH approved dust mask during all job activities. Closed transfer is required for treating cereal seeds in commercial seed treatment facilities. Taking into consideration these label statements, the number of applications and the expectation of the exposure period for handlers and workers, the risk to these individuals is not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Sedaxane Is Introduced Into the Environment?

When sedaxane is introduced into the environment as a seed treatment for canola and cereal grains it will adsorb to soil or be taken up into growing plants.

Based on the physical, chemical properties of sedaxane and environmental fate data, limited movement in soil is expected and leaching into groundwater or runoff into surface water is not predicted. Although birds and mammals may be exposed to sedaxane if they feed on treated seed, a risk assessment has shown that sedaxane poses practically no risk to birds or mammals even if a high amount of treated seed is ingested. Although Sedaxane is moderately to highly toxic to aquatic organisms, when sedaxane is used as a seed treatment limited exposure to the aquatic environment is expected.

Value Considerations

What Is the Value of Sedaxane 500FS Fungicide, A17511B Seed Treatment, and A16874F Seed Treatment?

Sedaxane 500FS Fungicide, A17511B Seed Treatment, and A16874F Seed Treatment are preventative seed treatments effective in the control or suppression of seed and soil-borne diseases in crops.

Sedaxane 500FS Fungicide, A17511B Seed Treatment, and A16874F Seed Treatment provide effective solutions to manage commercially important diseases such as rots (seed, root, crown, and foot), seedling blights, damping-off, seed-borne septoria, smuts, bunts and take-all. The multiple modes of fungicidal action found in A17511B Seed Treatment, and A16874F Seed Treatment provide benefits in terms of disease resistance management along with increased spectrum of disease protection. Moreover, because of recommended tank-mixes on all of the three products' labels and the insecticidal active ingredient in A17511B Seed Treatment, these three products provide options for simultaneous management of certain insect pests and fungal diseases.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures on the labels of A17511B Seed Treatment, A16874F Seed Treatment and Sedaxane 500FS Fungicide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a concern with users coming into direct contact with Sedaxane 500FS Fungicide, A17511B Seed Treatment and A16874F Seed Treatment on the skin or through inhalation of spray mists and dust, the label specifies that workers treating seed and handling treated seed must wear the following PPE. In commercial seed treatment facilities, workers treating, bagging, sewing, stacking, and forklifting treated seed must wear cotton coveralls over a long-sleeved shirt and long pants and chemical-resistant gloves. In addition, workers cleaning treatment equipment in commercial seed treatment facilities must wear chemical-resistant coveralls over a long-sleeved shirt and long pants and chemical-resistant gloves. Workers treating on-farm and/or planting treated seed must wear a long-sleeved shirt, long pants and chemical-resistant gloves. For good hygiene purposes, it is also recommended for workers to wear a NIOSH approved dust mask during all job activities. Closed transfer is required for treating cereal seeds in commercial seed treatment facilities.

What Additional Scientific Information Is Being Requested?

Although the risks and value have been found acceptable when all risk-reduction measures are followed, the applicant must submit additional scientific information as a condition of registration. More details are presented in the Science Evaluation of this Evaluation Report or in the Section 12 Notice associated with these conditional registrations. The applicant must submit the following information within the time frames indicated.

Human Health

- DACO 4.3.6 – Short-term inhalation toxicity study in rats.
- DACO 4.5.1, 4.8 – Low and mid-dose assessments of ovarian follicle counts in the 2-generation reproductive toxicity study in rats.
- The final freezer storage stability study reports for sedaxane metabolites in crop commodities up to 24 months (Report T014683-05-REG), and for sedaxane residues in processed commodities up to 12 months (Report KP-2009-02) are required to support the maximum storage intervals of samples from the magnitude of the residues studies.

Other Information

As these conditional registrations relate to a decision on which the public must be consulted,[3] the PMRA will publish a consultation document when there is a proposed decision on applications to convert the conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

The test data cited in this Evaluation Report (i.e. the test data relevant in supporting the registration decision) will be made available for public inspection when the decision is made to convert the conditional registrations to full registrations or to renew the conditional registrations (following public consultation). If more information is required, please contact the PMRA's Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

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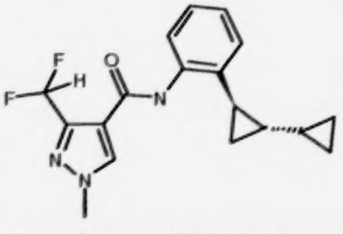
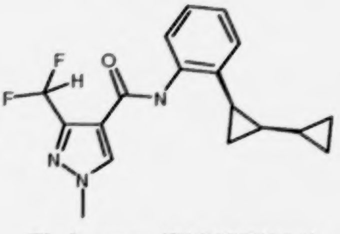
[3] As per subsection 28(1) of the *Pest Control Products Act*.

Science Evaluation

Sedaxane

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Sedaxane
Function	Fungicide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	mixture of 2 *cis*-isomers 2′-[(1*RS*,2*RS*)-1,1′-bicycloprop-2-yl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxanilide and 2 *trans*-isomers 2′-[(1*RS*,2*SR*)-1,1′-bicycloprop-2-yl]-3-(difluoromethyl)-1-methylpyrazole-4-carboxanilide
2. Chemical Abstracts Service (CAS)	1*H*-pyrazole-4-carboxamide, *N*-[2-[1,1'-bicyclopropyl]-2-ylphenyl]-3-(difluoromethyl)-1-methyl-
CAS number	874967-67-6 (trans isomer: 599197-38-3 / cis isomer: 599194-51-1)
Molecular formula	$C_{18}H_{19}F_2N_3O$
Molecular weight	331.4
Structural formula	 Trans isomer (SYN508210) (racemate of enantiomers)  Cis isomer (SYN508211) (racemate of enantiomers)
Purity of the active ingredient	98.0%

1.2 Physical and Chemical Properties of the Active Ingredient and End-use Product

Technical Product—Sedaxane Technical

Property	Result
Colour and physical state	Grey-beige solid
Odour	Weak, aromatic
Melting point	121.4°C
Boiling point or range	> 270°C
Density	1.23×10^3 kg/m^3 at 20°C
Vapour pressure at 20°C	6.5×10^{-8} Pa
Henry's law constant at 20°C	6.318×10^9
Ultraviolet (UV)-visible spectrum	Solution — λ [nm] — ε [L/mol × cm] Neutral — 215 — 22068 225 — 17233 265 — 5996 295 — 874 Acidic — 215 — 21860 225 — 17423 265 — 5683 295 — 851 Basic — 216 — 21271 225 — 17393 265 — 5833 295 — 955 No absorption maximum between 340 nm and 750 nm was observed
Solubility in water at 25°C	14 mg/L
Solubility in organic solvents at 25°C (g/L)	Solvent — Solubility Acetone — 410 Dichloromethane — 500 Ethyl acetate — 200 Hexane — 0.41 Methanol — 110 Octanol — 20 Toluene — 70
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = 3.3
Dissociation constant (pK_a)	No pK_a was found in the range of 1.0 to 12.0
Stability (temperature, metal)	Stable in nitrogen or air. Stable in the presence of aluminium, iron, aluminium acetate and iron(II) acetate.

End-use Product—A17511B Seed Treatment

Property	Result
Colour	Red
Odour	Very faint paint
Physical state	Liquid
Formulation type	Suspension
Guarantee	Difenoconazole 36.9 g/L nominal Thiamethoxam 30.7 g/L nominal Metalaxyl-M 9.5 g/L nominal Sedaxane 8 g/L nominal
Container material and description	1-1050 L plastic jugs or totes
Density	1.106 g/cm^3 at 20°C
pH of 1% dispersion in water	6.2
Oxidizing or reducing action	Not an oxidizing substance; not compatible with oxidizing agents
Storage stability	Stable at 20°C and a relative humidity of 50% for 14 months in fluorinated and non-fluorinated HDPE
Corrosion characteristics	No physical changes in the fluorinated and non-fluorinated HDPE test containers when stored at 20°C and a relative humidity of 50% for 14 months
Explodability	Product is not explosive

End-use Product—A16874F Seed Treatment

Property	Result
Colour	Red
Odour	Faint paint/weak aromatic
Physical state	Liquid
Formulation type	Suspension
Guarantee	Difenoconazole 66.2 g/L nominal Metalaxyl-M 16.5 g/L nominal Sedaxane 13.8 g/L nominal
Container material and description	1-1050 L plastic jugs or totes
Density	1.124 g/cm^3 at 20°C
pH of 1% dispersion in water	6.7-6.9
Oxidizing or reducing action	Not an oxidizing substance; not compatible with oxidizing agents
Storage stability	Stable at ambient temperature and relative humidity of 50% for one year in non-fluorinated HDPE
Corrosion characteristics	No physical changes in the appearance of the packaging material (non-fluorinated HDPE) after one year at ambient temperature and relative humidity of 50%
Explodability	Product is not explosive

End-use Product—SEDAXANE 500FS Fungicide

Property	Result
Colour	Beige
Odour	Aromatic
Physical state	Liquid
Formulation type	Suspension
Guarantee	500 g/L nominal
Container material and description	1-1050 L plastic jugs or totes
Density	1.167 g/cm^3 at 20°C
pH of 1% dispersion in water	6.70
Oxidizing or reducing action	Not an oxidizing or reducing substance
Storage stability	Stable at ambient temperature for at least one year in non-fluorinated HDPE
Corrosion characteristics	No physical changes in the non-fluorinated HDPE container during the one year storage stability study
Explodability	Product is not explosive

1.3 Directions for Use

Sedaxane 500FS Fungicide, A17511B Seed Treatment, and A16874F Seed Treatment, are used for the control or suppression of seed and soil-borne diseases including rots (seed, root, crown, and foot), seedling blights, damping-off, seed-borne septoria, smuts, bunts and take-all on various cereal crops, canola, and soybean. A17511B Seed Treatment also contains an insecticide and is used to suppress/control wireworm activity on certain cereal crops. The products are preventative in nature as they are applied to seed before planting. Product application rates per 100 kg of seed range from 325-650 mL for A17511B Seed Treatment, 180-360 mL for A16874F Seed Treatment, and 5-10 mL of Sedaxane 500FS Fungicide. It should be noted that all of these product application rates provide the same amount of the active ingredient sedaxane per 100 kg of seed, i.e. 2.5-5.0 g. Various tank mixes are recommended for additional disease or insect control.

1.4 Mode of Action

Sedaxane disrupts the normal respiration process in target fungal cells by inhibiting mitochondrial functioning. It is an effective preventative active ingredient with some systemic activity. Uniform and complete seed coverage is necessary to ensure the highest level of disease protection.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and the impurities in Sedaxane Technical have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The methods provided for the analysis of the active ingredient(s) in the formulations have been validated and assessed to be acceptable for use as enforcement analytical methods.

2.3 Methods for Residue Analysis

High-performance liquid chromatography methods with tandem mass spectrometry (HPLC-MS/MS) were developed and proposed for data generation and enforcement purposes. These methods fulfilled the requirements with regards to selectivity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in environmental media. Methods for residue analysis are summarized in Appendix I, Table 1.

The liquid chromatography analytical methods with tandem mass spectrometry (LC-MS/MS) GRM023.01A and GRM023.01B for the determination of sedaxane as the two isomers SYN508210 (trans) and SYN508211 (cis) in crop commodities; GRM023.03A for the determination of sedaxane as the two isomers SYN508210 and SYN508211, and the metabolites CSCD667584, CSCD658906, CSCD659089, CSCD668403, CSCD667555, CSCD465008 and CSCC210616 in crop commodities; GRM023.11A for the determination of sedaxane as the two isomers SYN508210 and SYN508211, and the metabolites CSCD659089, CSCD668403, CSCD659087, CSAA798670 and CSCD465008 in rotational crop commodities; GRM023.12A for the determination of CSCD465008 in soybean seed; and GRM006.08A for the determination of CSCD465008 and CSAA798670 in crop commodities are each acceptable for data gathering purposes. The extraction efficiencies of the methods were demonstrated. Specht (QuEChERs) multiresidue method P-14.141 (LC-MS/MS) is suitable for the enforcement of sedaxane, determined as the two sedaxane isomers SYN508210 and SYN508211 in crop commodities, based on acceptable method validation data and validation by an independent laboratory.

GRM023.10A (LC-MS/MS) is suitable for enforcement of sedaxane as the two isomers SYN508210 and SYN508211, and the metabolites CSCD658906 and CSCD659087 in livestock commodities, based on acceptable validation data, validation by an independent laboratory and demonstration of the extraction efficiency. Specht (QuEChERs) multiresidue method P-14.141 (LC-MS/MS) is suitable for the enforcement of sedaxane as the two isomers SYN508210 and SYN508211 in livestock commodities, based on acceptable validation data and validation by an independent laboratory.

The two isomers of sedaxane, SYN508210 and SYN508211, and the four plant metabolites CSCD667854, CSCD658906, CSCD667555 and CSCD465008 were subjected to the United States Food and Drug Administration MRM protocols (PAM I), and the methods were deemed inadequate to determine residues of sedaxane and the four specified metabolites.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for sedaxane was conducted. The database is comprehensive. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to sedaxane. However, a short-term inhalation toxicity study and ovarian follicle counts at the low and mid dose levels in a 2-generation reproductive toxicity study were not provided, and are being requested as conditions of registration. With the above exception, the studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices.

Sedaxane is a mitochondrial succinate dehydrogenase inhibitor, belonging to the pyrazole carboxamide class of pesticides. It is comprised of a mixture of trans and cis isomers at a ratio of 81-85% trans and 10-15% cis.

In a 28-day comparative toxicity study in rats of the trans isomer, cis isomer and a racemic 1:1 mixture of sedaxane, treatment-related increases in 16β-hydroxy testosterone hydroxylation were observed, suggesting that these compounds may be inducers of CYP 2B metabolizing enzymes. The three test compounds caused decreased 16α and 2α hydroxy-testosterone hydroxylation in males but increases in females; both 16α and 2α are markers for the cytochrome isoenzyme CYP 2C11. The above findings were supported by increased CYP 2B and CYP 3A protein contents. The weakly elevated ethoxyresorufin-O-dealkylase (EROD) activity suggests that the individual isomers and a 1:1 isomeric mixture of sedaxane do not act as polycyclic aromatic hydrocarbon-type inducers. Further toxicokinetic analyses indicated similar profiles between the trans and cis isomers.

Oral metabolism studies with radiolabelled sedaxane in rats demonstrated that it is rapidly absorbed, extensively metabolized, and excreted primarily in the feces/bile after single doses of 1 or 80 mg/kg bw, or repeated doses of 1 mg/kg bw/day over 14 days. After a single dose, maximum plasma concentrations of total radioactivity were achieved at 1-6 h post dose and declined with estimated terminal half-life values ranging from 23-29 hours. Similar terminal half-life values of 21-40 hours were obtained for blood. There were no apparent differences in the pharmacokinetics for blood and plasma between the dose levels. Sedaxane was rapidly and widely distributed in the body. The highest radioactive residues, other than the gastrointestinal tract, were observed in the kidney, liver and fat within 5 hours of dosing. Total radioactivity remaining in the carcass was low at 96 hours after a single oral dose. With repeated dosing, there were small increases in the residues in the liver and kidney, compared to single dose administration. Following the cessation of dosing, all tissue concentrations declined and there was no evidence of bioaccumulation. Concentrations of radioactivity were only measurable at low levels in the liver, kidney and spleen at the final sampling time (day 42 after the 14th dose). There were no major sex- or dose-related differences in tissue distribution profiles. The main metabolic pathways involved demethylation, hydroxylation, oxidation and conjugation, affording an array of hydroxylated metabolites and metabolites formed by cleavage of the terminal cyclopropyl moiety. An equivalent range of metabolites of desmethyl sedaxane were also formed. The major fecal/biliary metabolites were identified as trans para phenol and desmethyl trans para phenol metabolites, which together with the equivalent cis para phenol isomers accounted for approximately half of the administered dose (AD). Low levels (<1% AD) of a pyrazole amide metabolite were also detected in bile samples. The phenolic and hydroxy metabolites of sedaxane and desmethyl sedaxane were subject to glucuronic acid, sulphate and glutathione conjugation. Unchanged parent represented less than 10% of the administered dose in excreta. There were no major sex or dose related differences apparent in the qualitative metabolite profile for sedaxane. Elimination of sedaxane via respired volatiles or CO_2 was negligible.

Sedaxane and its associated end-use products, A17511B Seed Treatment (containing sedaxane, difenoconazole, metalaxyl-m and thiamethoxam), A16874F Seed Treatment (containing sedaxane, difenoconazole and metalaxyl-m) and Sedaxane 500FS Fungicide (containing sedaxane) were of low acute toxicity by the oral, dermal and inhalation routes of exposure in rats. They were minimally irritating to the eyes and non-irritating to the skin in rabbits, and were not dermal sensitizers in guinea pigs.

After 28 days of sedaxane dermal dosing in rats, no treatment-related dermal or systemic toxicity was observed at 1000 mg/kg bw/day.

A waiver request for a 90-day inhalation toxicity study in rats was submitted. Sedaxane is of low acute toxicity via the inhalation route of exposure in rats and has low vapour pressure. However, it still has the potential to form an aerosol during its use. Therefore, the 90-day inhalation toxicity study waiver was not granted and a 90-day rat inhalation toxicity study is required for sedaxane.

Following short-term repeated oral dosing in mice, decreased body weight, body weight gains and food efficiency, reduced bilirubin levels and increased liver and testes weights were observed in males at the limit dose. There were no treatment-related observations in female mice. In rats, the primary targets were the liver and thyroid after short-term dosing. In conjunction with body weight and food efficiency effects, there were also changes in clinical chemistry parameters (increased triglycerides, total protein, albumin and cholesterol levels), increased liver weights and histological effects such as hepatocyte pigmentation and centrilobular hepatocellular hypertrophy at higher doses. Treatment-related thyroid effects included decreased organ weights and follicular cell hypertrophy, predominantly in male rats. Decreased forelimb and/or hindlimb grip strength was observed in both sexes.

Following short-term repeated oral dosing in dogs, the primary target of sedaxane toxicity was the hematological system, including the spleen. In a 90-day toxicity study, decreased leukocytes, lymphocyte and/or monocyte counts were observed in females at the mid and high dose levels, while decreased spleen weights and cholesterol levels were seen in both sexes at the high dose. Decreased body weight and body weight gains (preceded by body weight loss) were observed down to the lowest dose tested in females (50 mg/kg bw/day) but were considered to be an equivocal effect since there were no body weight effects observed in the first 90 days of the 12 month toxicity study at the same dose level and 50 mg/kg bw/day was the NOAEL after a longer duration of dosing. Therefore, there was low concern for a lack of a NOAEL in female dogs after 90 days of sedaxane treatment. In a 12 month toxicity study in dogs, treatment-related decreased body weights, body weight gains and food consumption, reduced cholesterol levels, decreased spleen weights and decreased testes weights were observed.

Following long-term dosing, decreased body weight, body weight gains and food efficiency were observed in mice and rats.

In a mouse oncogenicity study, statistically significant increases in hepatocellular adenomas and carcinomas were observed in the livers of male mice at the highest dose tested. The incidences of liver adenomas, carcinomas and combined adenomas and carcinomas exceeded the laboratory historical control ranges and there was no other corroborative liver histopathology observed. Other than the appearance of liver tumours, there was no durational effect of dosing observed in mice.

In a 104/105 week rat combined chronic/oncogenicity study in rats, treatment-related effects included thyroid follicular cell hypertrophy, follicular cell hyperplasia, epithelial desquamation and basophilic colloid. In the liver, the histological effects observed after 2 years were similar to those observed after short-term dosing, except for increased eosinophilic cell foci which were only noted after two years of sedaxane treatment. Decreased hindlimb grip strength was observed only in males in the long-term study. Other treatment-related findings included increases in thymus epithelial tubular hyperplasia and kidney inflammation/inflammatory cell infiltration, as well as decreased vaginal mucification in females. When compared to the short-term toxicity studies, there was an increased variety of thyroid histological lesions observed in rats at lower dose levels in the long-term study, suggesting a durational effect of dosing. Increased incidences of hepatocellular adenomas in the liver and follicular cell adenomas and carcinomas in the thyroid were observed in males at the high dose level. There was no corroborative liver histopathology but the thyroid tumours were associated with non-neoplastic lesions in the thyroid (follicular cell hyperplasia). In female rats, treatment-related uterine adenocarcinomas were observed at the highest dose tested. The incidence fell within the laboratory's historical control range, but it exceeded the incidence observed in 4 out of 5 control studies provided. In the absence of cancer mode of action information for any tumour type, a quantitative linear low dose extrapolation (Q_1*) approach was used to analyze the tumour responses, and the incidence of uterine adenocarcinomas in rats was selected for the cancer risk assessment as it was the highest value of the four tumour types.

Sedaxane was not genotoxic in a standard battery of in vitro and in vivo assays.

In a 2-generation reproductive toxicity study in rats, treatment-related effects in the parental animals consisted of decreased body weights, body weight gains and food consumption, as well as increased liver weights. There was evidence of reproductive toxicity. Treatment-related decreased ovarian weights, reductions in ovarian follicle counts (primordial, growing, antral, corpora lutea) and an increased number of females in lactational diestrus (i.e. not cycling) were observed at the highest dose tested. The applicant considered the differences in ovarian follicle and corpora lutea counts to be an indirect consequence of high dose effects on pup and maternal body weights and the increased number of dams in lactational diestrus. Review of the individual animal data did not show a clear correlation between the presence of lactational diestrus in dams and decreased ovarian follicle counts. Amongst the high dose females assessed, only 4 of them were in lactational diestrus and of those females, only one animal appeared to have lower ovarian follicle counts compared to controls and cycling females in the same dose group. The remaining females in the high dose group were cycling and had decreased ovarian follicle counts compared to the concurrent controls. Overall, based on the weight of evidence of related ovarian effects occurring at the high dose level in this 2-generation reproductive toxicity study and the presence of treatment-related endocrine effects in the sedaxane toxicological database, the changes in ovarian follicle counts were considered to be treatment-related and adverse. Low and mid dose ovarian follicle counts were not performed, which precluded the establishment of NOAEL for this endpoint; therefore, these data have been requested. In the meantime, a database uncertainty factor (UF_{DB}) has been applied to risk scenarios involving repeated exposure. Decreased pup body weights, delayed vaginal patency, increased anogenital distance in females, increased liver weights and decreased spleen weights were noted in offspring at the same dose level that parental effects were observed. The effects on sexual maturation were considered to be equivocal since the changes from controls were marginal.

In a rat developmental toxicity study, treatment-related maternal effects included decreased body weight gain or body weight loss, and decreased food consumption. No developmental toxicity (including teratogenicity) was observed up to the highest dose tested. In a rabbit developmental toxicity study, decreased maternal body weight gains or body weight loss, and decreased food consumption were noted. A slightly increased incidence of late-gestation abortions (incidences of 0, 1, 1, 2 in the control, low, mid, high doses respectively) and decreased fetal weights occurred at the same dose level where maternal toxicity was observed. There was no evidence of teratogenicity in rabbits. The abortions could not be specifically attributed to maternal or developmental toxicity and were not considered to represent a fetal sensitivity.

In an acute neurotoxicity study in rats, treatment-related functional effects included piloerection, reduced activity and decreased rearing in both sexes, ruffled fur and recumbency in males, and weakened condition, swaying gait, decreased activity, reduced muscle tone and decreased locomotor activity in females. In a rat subchronic neurotoxicity study, treatment-related decreased body weight, body weight gains, food consumption and food efficiency, along with decreased locomotor activity were observed in both sexes at the highest dose tested. There was no treatment-related histopathology observed in the central or peripheral nervous system in either of the neurotoxicity studies.

In a 28-day immunotoxicity study, sedaxane did not cause immunosuppression in male mice; however, increased spleen and thymus weights and increased IgM antibody-forming cells were observed at the limit dose. There was no histopathology observed. The toxicological significance of these findings is not known. The high coefficients of variation noted for the IgM data decreased the confidence in these results. A review of other repeat-dose toxicity studies indicated that immune effects generally occurred at high doses. In the 90-day and 12-month dog toxicity studies, decreased leukocyte parameters were noted in both sexes, while in the 2-generation reproductive toxicity study, decreased spleen weights were observed in offspring. In the 2-year combined chronic/oncogenicity study in rats, treatment-related increases in thymic epithelial hyperplasia were noted in females. Decreased thymus weights were observed after treatment with the cis isomer of sedaxane in females. Based on the weight of evidence, there were no residual concerns regarding immunotoxicity after sedaxane treatment.

Studies conducted with a major crop metabolite and aerobic soil transformation product, CSCD465008 (3-(difluoromethyl)-1H-pyrazole-4-carboxylic acid) indicated that it is of low acute toxicity via the oral route in rats and not genotoxic in bacteria, mouse lymphoma cells or human lymphocytes. After short-term oral dosing with CSCD465008, there were no treatment-related effects up to the limit dose in rats. Overall, these results suggest that the CSCD465008 metabolite is not more toxic than sedaxane.

Results of the toxicology studies conducted on laboratory animals with sedaxane, one related metabolite and associated sedaxane end-use products are summarized in Appendix I, Tables 2 and 3. The toxicology endpoints for use in the human health risk assessment are summarized in Appendix I, Table 4.

Incident Reports
Since April 26, 2007, registrants have been required by law to report incidents, including adverse effects to health and the environment, to the PMRA within a set time frame. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of Health Canada's website. Incidents from Canada and the United States were searched for sedaxane, and any additional information submitted by the applicant during the review process was considered. As of December 5, 2011, there were no health-related incident reports for this active in the PMRA Incident Reporting database.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for sedaxane. The database contains the full complement of required studies including developmental toxicity studies in rats and rabbits and a reproductive toxicity study in rats. In the 2-generation reproductive toxicity study, there is residual uncertainty surrounding a critical endpoint, decreased ovarian follicle counts, since low and mid dose assessments were not performed and a NOAEL could not be established. This residual uncertainty has been addressed through the use of a database uncertainty factor (UF_{DB}) for repeated exposure scenarios.

With respect to potential prenatal and postnatal toxicity, there was no indication of increased susceptibility of the young compared to parental animals in the reproductive toxicity study. Vaginal opening was delayed and anogenital distance was increased in female offspring at the highest dose tested; however, these effects were marginal, occurring in the presence of maternal toxicity (liver, ovary and body weight effects) and were not considered to represent a serious effect. There were no treatment-related effects in the rat developmental toxicity study. A marginally increased incidence of late abortions was observed at the highest dose tested in the rabbit developmental toxicity study. Although abortions are considered a serious developmental endpoint, the level of concern was tempered by the presence of maternal toxicity (body weight loss, decreased or no food consumption, reduced defecation), the low incidence of this finding, and the singular incidences of abortions in the laboratory's historical control database. The NOAEL of 100 mg/kg bw/day for abortions in the rabbit developmental toxicity study was considered to be a conservative endpoint and is considered to be sufficiently conservative to account for seriousness of the endpoint. Overall, there is a low concern for sensitivity of the young and effects on the young are well-characterized. Therefore, the *Pest Control Products Act* factor has been reduced to 1-fold.

3.2 Acute Reference Dose (ARfD)

General Population

To estimate acute dietary risk (1 day), the acute neurotoxicity study with a NOAEL of 30 mg/kg bw was selected for risk assessment. At the LOAEL of 250 mg/kg bw, piloerection, reduced activity, initial inactivity and decreased rearing were observed in both sexes, ruffled fur, recumbency, as well as decreased body weight, body weight gain and food consumption were observed in males and weakened condition, swaying gait, decreased activity, reduced muscle tone, as well as decreased locomotor activity were observed in females. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor has been reduced to 1-fold. **The composite assessment factor (CAF) is 100-fold.**

The ARfD is calculated according to the following formula:

$$\text{ARfD (gen. pop)} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{30 \text{ mg/kg bw}}{100} = 0.3 \text{ mg/kg bw of sedaxane}$$

The ARfD provides a margin of 333 to the NOAEL for developmental toxicity in the rabbit and is thus considered protective of pregnant women and their fetuses.

3.3 Acceptable Daily Intake (ADI)

To estimate dietary risk of repeat exposure, the 2-generation reproductive toxicity study with a point of departure (POD) of 18 mg/kg bw/day was selected for risk assessment. At 143 mg/kg bw/day, decreased ovarian weights and decreased primordial follicles (P generation), growing and antral follicles (F_1 generation) and corpora lutea (P and F_1 generations) counts and increased females in lactational diestrous were observed. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability have been applied. As discussed above, there is residual uncertainty surrounding the ovarian follicle counts since low and mid dose assessments were not performed and a NOAEL could not be established. Accordingly, a 3-fold UF_{DB} has been applied to the lowest dose tested in the 2-generation reproductive toxicity study. This results in a lower point of departure than the 2-year combined chronic/oncogenicity study in rats. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. **The composite assessment factor (CAF) is 300-fold.**

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{POD}}{\text{CAF}} = \frac{18 \text{ mg/kg bw/day}}{300} = 0.06 \text{ mg/kg bw/day of sedaxane}$$

The ADI provides a margin of 3333 to the dose at which a marginal increase in abortions occurred in rabbits and 2383 to the dose at which decreased spleen weights were observed in offspring in the 2-generation reproductive toxicity study.

Cancer Assessment

Sedaxane exhibits oncogenic potential. There were treatment-related thyroid follicular cell tumours and hepatocellular tumours in male rats, uterine adenocarcinomas in female rats and hepatocellular tumours in male mice. No mode of action information was provided for any of the tumour types. An adjusted unit risk value (Q_1*) of 3.81×10^{-3} $(\text{mg/kg bw/day})^{-1}$ for uterine adenocarcinomas in female rats was used for the cancer risk assessment as it was the highest value of the four tumour types.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Short-, Intermediate-term Dermal

For short- and intermediate-term dermal risk assessment for adults, the 2-generation reproductive toxicity study in rats was selected. The existing short-term dermal toxicity study did not address the endpoint of concern thus necessitating the use of an oral study for risk assessment. At 143 mg/kg bw/day, decreased ovarian weights, decreased ovarian weights and decreased primordial follicles (P generation), growing and antral follicles (F_1 generation) and corpora lutea (P and F_1 generations) counts and increased females in lactational diestrous were observed. The point of departure was 18 mg/kg bw/day.

For occupational scenarios, the target Margin of Exposure (MOE) selected for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability, along with an additional 3-fold uncertainty factor for database deficiency. This target MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

Short-, Intermediate-term Inhalation

For short- and intermediate-term inhalation risk assessment for adults, the 2-generation reproductive toxicity study in rats was selected. A short-term inhalation study was not available and therefore, an oral study was used for the risk assessment. At 143 mg/kg bw/day, decreased ovarian weights and decreased primordial follicles (P generation), growing and antral follicles (F_1 generation) and corpora lutea (P and F_1 generations) counts and increased females in lactational diestrous were observed. The point of departure was 18 mg/kg bw/day.

For occupational scenarios, the target MOE selected for this endpoint is 300. Ten-fold factors were applied each for interspecies extrapolation and intraspecies variability, along with an additional 3-fold uncertainty factor for database deficiency. This target MOE is considered to be protective of all populations, including nursing infants and the unborn children of exposed female workers.

3.4.2 Toxicological Endpoints

Occupational exposure to Sedaxane 500 FS Fungicide, A17511B Seed Treatment and A16874F Seed Treatment is characterized as short- to intermediate-term and is predominantly by the dermal and inhalation routes.

3.4.2.1 Dermal Absorption

In support of the registration of Sedaxane 500FS Fungicide, A17511B Seed Treatment and A16874F Seed Treatment, the applicant submitted an in vivo dermal absorption study in rats and an in vitro dermal absorption study in rat and human skin. Together, these studies are referred to as a "triple pack". The submitted dermal penetration studies for sedaxane were of good quality and the 'triple pack' approach was considered for setting a dermal absorption value.

The three in vivo and in vitro dermal absorption studies were compared. The two in vitro studies were conducted with the same doses and conditions; therefore, the rat and human in vitro studies could be directly compared. The results of the in vitro studies showed that rat skin membranes are more permeable to sedaxane than human skin membranes. Comparing the in vivo and the in vitro studies, the doses used in the in vivo and in vitro studies were similar (approximately 5100, 250 and 25 $\mu g/cm^2$ for the high, mid and low dose, respectively). However, the exposure duration used for the in vitro studies was 24 hours, which is different from the rat in vivo study (6 hours). Therefore, the results from the rat in vivo study and the rat in vitro study cannot be directly compared. As such, a "triple pack" approach could not be supported.

However, a dermal absorption could be derived from the rat in vivo study. Given the variability in actual deposition under field conditions, it is considered appropriate to derive an estimate of dermal absorption based on the low dose groups, as percent dermal absorption was greatest at the low dose level. In addition, since a longer post-exposure period provides more information about the fate of absorbable and absorbed dose over time, the dermal absorption was derived based on groups sacrificed at 120 hours. The dermal absorption estimate of 7% from the low dose group at 120 hours sacrifice was considered most appropriate to adopt for risk assessment purposes. Adopting 7% as the dermal absorption value for sedaxane is regarded as conservative since approximately 29% of this value was retained on the skin and it is unlikely that all of the skin residues will become systemically available.

3.4.3 Occupational Exposure and Risk

Canola and soybean seed can be treated with Sedaxane 500FS Fungicide in commercial seed treatment facilities. Cereal seed (barley, wheat, oat, rye and triticale) can be treated with Sedaxane 500FS Fungicide, A17511B Seed Treatment or A16874F Seed Treatment, both in commercial seed treatment facilities and on-farm.

3.4.3.1 Commercial Seed Treatment Exposure

Individuals have potential for exposure to Sedaxane 500FS Fungicide, A17511B Seed Treatment and A16874F Seed Treatment, while treating seed in commercial seed treatment facilities. Chemical specific data for assessing human exposure during commercial seed treatment were not submitted. As such, surrogate exposure data have been used to estimate risk to workers in commercial seed treatment facilities.

3.4.3.1.1 Canola and Soybean Seed

Sedaxane 500FS Fungicide will be available in open jugs and for low-capacity commercial seed treatment facilities or closed transfer containers for high-capacity seed treatment operations. As such, worker exposure from seed treatment in both open pour and closed transfer commercial facilities were assessed.

For assessing seed treatment in low-capacity commercial facilities, the surrogate study used in the risk assessment was conducted in open pour commercial facilities. In the study, workers were treating soybean seed with Apron FL, containing 33% metalaxyl, at a target rate of 30 g a.i./100 kg seed. The average replicate length was approximately 3 hours. The following tasks were monitored: mixer/operator, bagger, and bag sewer. Three replicates were monitored per task. Dermal exposure for each worker was measured by passive dosimetry using a combination of an inner whole body dosimeter, hand rinses, and face/neck wipes. The inner dosimeter was worn underneath long clothes. All workers wore one layer of clothing and some wore more layers for warmth. Mixer/operators also wore goggles, chemical resistant gloves and aprons. Baggers wore thick cotton gloves for warmth. Some workers wore dust masks. Inhalation exposure for each worker was measured by means of a personal air sampling pump with a sampler consisting of a XAD-2 vapour collection tube and two glass fibre filters. Exposure values were normalized for the amount of active ingredient handled. The 90th percentile values from the Apron FL study were used in the risk assessment because of study limitations (small sample sizes, clothing and QA/QC irregularities).

For assessing seed treatment in high-capacity seed treatment operations, the surrogate study used in the risk assessment was conducted in 5 Canadian large closed-transfer commercial seed treatment facilities. In the study, workers were treating canola seed with Helix XTra Seed Treatment (Registration number 26638), containing thiamethoxam, at a target rate of 400 g a.i./100 kg seed. The average replicate length was approximately 9.65 hours. The following tasks were monitored: treating (n = 17), cleaning, bagging/sewing/stacking (n = 53) and forklift driving (n = 12). Dermal exposure for each worker was measured by passive dosimetry using a combination of an inner whole body dosimeter, hand rinses, and face/neck wipes. The inner dosimeter was worn underneath worker clothing. Treaters and cleaners wore chemical-resistant coveralls over a single layer and chemical-resistant gloves. Forklift drivers and bagger/sewer/stackers wore cotton coveralls over a single layer and chemical-resistant gloves. Inhalation exposure for each worker was measured by means of a personal air sampling pump with an OSHA Versatile Sampler (OVS) tube. Exposure values for treaters and bagger/sewer/stackers were normalized for the amount of active ingredient handled. Exposure values for cleaners were normalized for the application rate used in the study. However, it is uncertain that the normalized values are applicable for the Sedaxane 500FS Fungicide risk assessment, since there is a 80-fold difference between the application rates of the study (400 g a.i./100 kg seed) and the use of Sedaxane 500FS Fungicide (5 g a.i./100 kg). Therefore, risk estimates for cleaners were calculated using both the not normalized and normalized exposure values from the Helix study. For the Helix study, all phases were well conducted and reported and no significant limitations were identified. As such, arithmetic mean values were considered adequate for use in risk assessments.

The dust off data submitted by the applicant showed that canola seed treated with Sedaxane 500FS Fungicide + Helix Xtra was comparably dusty to the seed used in the two surrogate studies (soybean seed treated with Apron FL and canola seed treated with Helix Xtra). In addition, the dust off data showed that soybean seed treated with Sedaxane 500FS was less dusty than canola seed treated with Helix Xtra and comparably dusty to soybean seed treated with Apron FL. As such, the surrogate studies are not expected to underestimate exposure of the use from Sedaxane 500FS Fungicide on canola and soybean seed.

Tables 1 and 2 present the non-cancer and cancer risk estimates, respectively, for the commercial seed treatment of canola and soybean seed with Sedaxane 500FS Fungicide. The calculated margins of exposure (MOEs) were well above the target MOE of 300. Cancer risk for commercial workers treating canola and soybean seed was estimated by calculating the lifetime average daily dose (LADD). An exposure duration of 60 days was assumed for commercial treaters. Although this may be a high end estimate, this value was considered appropriate as soybean and canola seeds may be treated for several months. Calculated cancer risk estimates were less than 1×10^{-5}. As such, there are no risks of concern for treating canola and soybean seed with Sedaxane 500FS Fungicide in commercial facilities when workers wear the PPE worn in the surrogate studies. However, for treaters in closed transfer commercial seed treatment facilities, since calculated MOEs were well above the target MOE of 300 and cancer risk estimates were well below 1×10^{-5}, treaters are not required to wear chemical-resistant coveralls. Instead, treaters are required to wear cotton coveralls over a single layer and chemical-resistant gloves.

Table 1 Non-cancer risk estimates for workers treating canola and soybean seed in commercial facilities with Sedaxane 500FS Fungicide

Worker task	Unit exposure (µg/kg a.i. handled)[1]			Application rate (kg a.i./kg seed)	Seed treated (kg seed/ day)	Exposure (mg/kg bw/day)[3]	Calculated MOE[4]
	Dermal	Inhalation	Total[2]				
Small-scale open transfer commercial facilities (using Apron FL study unit exposure values)							
Canola							
Mixer/operator	211.49	4.85	19.65	0.00005	60000	8.42×10^{-4}	21400
Bagger	40.14	2.3	5.11	0.00005	60000	2.19×10^{-4}	82200
Bagger/sewer	96.1	37.21	43.94	0.00005	60000	1.88×10^{-3}	9560
Soybean							
Mixer/operator	211.49	4.85	19.65	0.00005	216000	3.03×10^{-3}	5940
Bagger	40.14	2.3	5.11	0.00005	216000	7.88×10^{-4}	22800
Bagger/sewer	96.1	37.21	43.94	0.00005	216000	6.78×10^{-3}	2660
Large-scale closed transfer commercial facilities (using Helix study unit exposure values)							
Canola							
Treater	7.36	0.27	0.785	0.00005	60000	3.37×10^{-5}	535000
Cleaner – not normalized*	19.4	1.54	2.90	0.00005	60000	2.90×10^{-3}	6210
Cleaner – normalized †	4.84×10^{-2}	3.84×10^{-3}	7.23×10^{-3}	0.00005	60000	3.58×10^{-5}	503000
Bagger/sewer/stacker	1.29	0.25	0.340	0.00005	60000	1.46×10^{-5}	1230000
Forklift operator	0.72	0.105	0.155	0.00005	60000	6.66×10^{-6}	2700000
Soybean							
Treater	7.36	0.27	0.785	0.00005	216000	1.21×10^{-4}	149000
Cleaner – not normalized*	19.4	1.54	2.90	0.00005	216000	2.90×10^{-3}	6210
Cleaner – normalized †	4.84×10^{-2}	3.84×10^{-3}	7.23×10^{-3}	0.00005	216000	3.58×10^{-5}	503000
Bagger/sewer/stacker	1.29	0.25	0.340	0.00005	216000	5.25×10^{-5}	343000
Forklift operator	0.72	0.105	0.155	0.00005	216000	2.40×10^{-5}	751000

[1] For small scale open transfer commercial facilities, the 90th percentile values of the Apron FL study on soybean seed were used. For large scale closed transfer commercial facilities, the arithmetic mean values were used from the Helix study.

[2] Total unit exposure = (Dermal unit exposure × 7% dermal absorption) + Inhalation unit exposure

[3] Exposure = (Total unit exposure × Application rate × Seed treated per day)/(70 kg bw × 1000 µg/mg)

[4] Based on NOAEL = 18 mg /kg bw/day, target MOE = 300

* Not normalized cleaner unit exposure values are in µg/kg bw/day; exposure = (total unit exposure)/(1000 µg/mg)

† Normalized cleaner unit exposure values are in (µg/kg bw/g a.i./100 kg seed); as such,
exposure = (total unit exposure × 5 g a.i./100 kg seed)/(1000 µg/mg)

Table 2 Cancer risk estimates for workers treating canola and soybean seed in commercial facilities with Sedaxane 500FS Fungicide

Worker task	ADD (mg/kg bw/day)[1]	Days of exposure	Working Duration (yrs)	LADD (mg/kg bw/day)[2]	Cancer Risk[3]
Small-scale open transfer commercial facilities (using Apron FL study unit exposure values)					
Canola					
Mixer/operator	8.42×10^{-4}	60	40	7.38×10^{-5}	3×10^{-7}
Bagger	2.19×10^{-4}	60	40	1.92×10^{-5}	7×10^{-8}
Bagger/sewer	1.88×10^{-3}	60	40	1.65×10^{-4}	6×10^{-7}
Soybean					
Mixer/operator	3.03×10^{-3}	60	40	2.66×10^{-4}	1×10^{-6}
Bagger	7.88×10^{-4}	60	40	6.91×10^{-5}	3×10^{-7}
Bagger/sewer	6.78×10^{-3}	60	40	5.94×10^{-4}	2×10^{-6}
Large-scale closed transfer commercial facilities (using Helix study unit exposure values)					
Canola					
Treater	3.37×10^{-5}	60	40	2.95×10^{-6}	1×10^{-8}
Cleaner – not normalized	2.90×10^{-3}	60	40	2.54×10^{-4}	1×10^{-6}
Cleaner – normalized	3.58×10^{-5}	60	40	3.14×10^{-6}	1×10^{-8}
Bagger/sewer/stacker	1.46×10^{-5}	60	40	1.28×10^{-6}	5×10^{-9}
Forklift operator	6.66×10^{-6}	60	40	5.84×10^{-7}	2×10^{-9}
Soybean					
Treater	1.21×10^{-4}	60	40	1.06×10^{-5}	4×10^{-8}
Cleaner – not normalized	2.90×10^{-3}	60	40	2.54×10^{-4}	1×10^{-6}
Cleaner – normalized	3.58×10^{-5}	60	40	3.14×10^{-6}	1×10^{-8}
Bagger/sewer/stacker	5.25×10^{-5}	60	40	4.60×10^{-6}	2×10^{-8}
Forklift operator	2.40×10^{-5}	60	40	2.10×10^{-6}	8×10^{-9}

[1] ADD = Absorbed daily dose = Exposure from Table 1

[2] LADD = Lifetime average daily dose = $\frac{(\text{ADD} \times \text{Days of exposure} \times \text{Working duration})}{(365 \text{ days/year} \times 75 \text{ years in lifetime})}$

[3] Based on $Q_1^* = 3.81\text{x}10^{-3}$ (mg/kg bw/day)$^{-1}$

3.4.3.1.2 Cereal Seed (Barley, Wheat, Oat, Rye and Triticale)

Cereals can be treated in commercial facilities. In eastern Canada, the majority of the cereal market (~85–90%) consists of certified seed that is cleaned and treated (as required) at commercial seed treatment facilities, whereas in western Canada only 20% consists of commercially treated cereal seed. As such, the majority of cereal seed treated in Canada is treated on-farm. Both commercial and on-farm seed treatment applications to cereals occur "just in time", where seed is treated in batches as it is planted. Typically, seed is treated as it is transferred from the grain truck or seed bin and is not bagged.

For assessing commercial treatment of cereal seed, the surrogate study used in the risk assessment was conducted in closed-transfer commercial facilities. In the study, workers were treating wheat seed with Jockey Fungicide, containing 167g/L fluquinconazole and 31.2 g/L prochloraz, at target rates of 75 and 14 g a.i./100 kg seed, respectively. The monitoring period for treaters (n = 7) and cleaners (n = 8) was less than 35 minutes, whereas the monitoring period for baggers (n = 22) ranged from 3 to 8 hours. Dermal exposure for each worker was measured by passive dosimetry using a combination of an inner whole body dosimeter, hand rinses, and face/neck wipes. The inner dosimeter was worn underneath worker clothing. Treaters wore a long-sleeved shirt, long pants and nitrile gloves. Cleaners wore Tyvek coveralls over a long-sleeved shirt, long pants and nitrile gloves. Baggers wore a long-sleeved shirt and long pants. Inhalation exposure for each worker was measured by means of a personal air sampling pump with an IOM multi-dust sampler with a glass fibre filter. Exposure values were normalized for the amount of active ingredient handled. Exposure values for cleaners were normalized for the application rate used in the study. Since the application rates from the study (14 g a.i./100 kg seed) and for the proposed use (5 g a.i./100 kg) are similar, risk estimates for cleaners were calculated using normalized exposure values from the Jockey study. In addition, cleaner exposure was monitored for only 9 – 33 minutes in the study; as such, the risk estimates for cleaner and treater were combined to take into account workers who conduct both tasks during the workday. For the Jockey study, the arithmetic mean was used for all activities since there was an adequate number of replicates and the recoveries were sufficient. The highest value of the two actives monitored in the surrogate study was chosen for risk assessment purposes since it should not underestimate exposure.

The submitted dust off study did not measure dust off potential of Jockey-treated wheat seed. However, dust off of wheat seed treated with other formulations was measured. Sedaxane 500FS Fungicide-treated barley and oat seed had higher dust off potential than Austral Plus Net, containing 42.1 g/L, -treated wheat seed (1.6x higher for barley and 3.4x higher for oats). As such, the Jockey study may underestimate the exposure for the use of barley and oat seed with Sedaxane 500FS Fungicide. The dust off potential for A17511B Seed Treatment-treated barley seed and A16874F Seed Treatment-treated barley seed is 3x and 5.4x lower than that for Austral Plus Net-treated wheat seed, respectively. In addition, the dust off potential for A17511B Seed Treatment-treated oat seed and A16874F Seed Treatment-treated oat seed is comparable to that of Austral Plus Net-treated wheat seed. Therefore, the Jockey study is not expected to underestimate the exposure for the use of barley and oat seed with either A17511B Seed Treatment or A16874F Seed Treatment. No dust off data were submitted for wheat, rye and triticale.

Tables 3 and 4 present the non-cancer and cancer risk estimates, respectively, for the commercial seed treatment of cereals with Sedaxane 500FS Fungicide, A17511B Seed Treatment or A16874F Seed Treatment. The calculated MOEs were well above the target MOE of 300. Cancer risk for commercial workers treating cereal seed was estimated by calculating the LADD. An exposure duration of 60 days was assumed for commercial treaters. Although this may be a high end estimate, this value was considered appropriate as cereal seed may be treated for several months. Calculated cancer risk estimates were less than 1×10^{-5}. As such, there are no risks of concern for treating cereal seed with Sedaxane 500FS Fungicide, A17511B Seed Treatment or A16874F Seed Treatment in closed transfer commercial facilities when workers wear the PPE worn in the surrogate studies. Given the high MOE and low cancer risk, it was determined that further confirmatory dust off data for wheat, rye and triticale were not required.

Table 3 Non-cancer risk estimates for workers treating cereal seed in commercial facilities with Sedaxane 500FS Fungicide, A17511B Seed Treatment or A16874F Seed Treatment

Worker task	Unit exposure (µg/kg a.i. handled)[1]			Application rate (kg a.i./kg seed)	Seed treated (kg seed/day)	Exposure (mg/kg bw/day)[3]	Calculated MOE[4]
	Dermal	Inhalation	Total[2]				
Closed transfer commercial facilities (using Jockey study unit exposure values)							
Cereals (barley, wheat, oats, rye, and triticale)							
Treater	0.88	0.016	0.078	0.00005	325700	1.81×10^{-5}	997000
Bagger	17.67	0.89	2.127	0.00005	325700	4.95×10^{-4}	36400
Cleaner*	18.46	0.64	1.93	0.00005	325700	1.38×10^{-4}	130000
Treater + Cleaner †	-	-	-	0.00005	325700	1.56×10^{-4}	115000

[1] For closed transfer commercial facilities, the arithmetic mean values were used from the Jockey study

[2] Total unit exposure = (Dermal unit exposure × 7% dermal absorption) + Inhalation unit exposure

[3] Exposure = (Total unit exposure × Application rate × Seed treated per day)/(70 kg bw × 1000 µg/mg)

[4] Based on NOAEL = 18 mg /kg bw/day, target MOE = 300

* Cleaner unit exposure values are in (µg/g a.i./100kg seed); as such,
exposure = (total unit exposure × 5 g a.i./100 kg seed)/(70 kg bw × 1000 µg/mg)

† Assuming that a worker both treats and cleans in the same workday.

Table 4. Cancer risk estimates for workers treating cereal seed in commercial facilities with Sedaxane 500FS Fungicide, A17511B Seed Treatment or A16874F Seed Treatment

Worker task	ADD (mg/kg bw/day)[1]	Days of exposure	Working Duration (yrs)	LADD (mg/kg bw/day)[2]	Cancer Risk[3]
Closed transfer commercial facilities (using Jockey study unit exposure values)					
Cereals (barley, wheat, oats, rye, and triticale)					
Treater	1.81×10^{-5}	60	40	1.58×10-6	6×10^{-9}
Bagger	4.95×10^{-4}	60	40	4.34×10^{-5}	2×10^{-7}
Cleaner	1.38×10^{-4}	60	40	1.21×10^{-5}	5×10^{-8}
Treater + Cleaner †	1.56×10^{-4}	60	40	1.37×10^{-5}	5×10^{-8}

[1] ADD = Absorbed daily dose = Exposure from Table 3

[2] LADD = Lifetime average daily dose = (ADD × Days of exposure × Working duration)
365 days/year × 75 years in lifetime)

[3] Based on $Q_1{}^* = 3.81\text{x}10^{-3}$ (mg/kg bw/day)$^{-1}$

3.4.3.2 On-Farm Seed Treatment Exposure

Individuals have potential for exposure to Sedaxane 500FS Fungicide, A17511B Seed Treatment and A16874F Seed Treatment while treating seed on-farm. Chemical specific data for assessing human exposure during on-farm seed treatment were not submitted. As such, surrogate exposure data have been used to estimate risk to workers in on-farm seed treatment facilities.

3.4.3.2.1 Canola and Soybean Seed

The registrant markets Sedaxane 500FS Fungicide to commercial canola and soybean seed treaters, as such, on-farm treatment of soybeans and canola with Sedaxane 500FS Fungicide was not assumed and not assessed.

3.4.3.2.2 Cereal Seed (Barley, Wheat, Oat, Rye and Triticale)

For on-farm seed treatment and planting of cereal seed, the Dividend 36FS, 3% difenconazole, study was considered appropriate to be used as a surrogate study in the risk assessment. The study measured 16 replicates treating and planting wheat seed on-farm. In all trials, wheat seed was treated with Dividend 36FS, containing difenoconazole, at a target rate of 24.8 g a.i./100 kg. Replicates were monitored for less than 3 hours to 8 hours. The product was open poured manually into the treatment equipment. Treated wheat seed was not bagged. Dermal exposure for each worker was measured by passive dosimetry using a combination of an inner whole body dosimeter, hand rinses, and face/neck wipes. The inner dosimeter was worn underneath worker clothing. Workers wore a single layer and neoprene gloves. Inhalation exposure was monitored using OVS samplers attached to a personal air sampling pump. The study had minor limitations and had acceptable field recoveries and sample size. As such, the arithmetic mean values from the study were adequate for risk assessment purposes.

The submitted dust off data showed that barley seed treated with Sedaxane 500FS Fungicide, A17511B Seed Treatment or A16874F Seed Treatment was less dusty than wheat seeds treated with Dividend 36FS. In addition, the dust off data showed that oat seed treated with Sedaxane 500FS Fungicide was comparably dusty to wheat seed treated with Dividend 36FS. Oat seed treated with A17511B Seed Treatment or A16874F Seed Treatment was approximately 3x less dusty than wheat seed treated with Dividend 36FS. Therefore, the Dividend 36FS surrogate study is not expected to underestimate on-farm exposure for barley and oats. However, dust off from wheat, rye and triticale seed treated with sedaxane-containing products was not measured in the submitted dust off study.

Tables 5 and 6 present the non-cancer and cancer risk estimates, respectively, for the on-farm treatment and planting with Sedaxane 500FS Fungicide, A17511B Seed Treatment or A16874F Seed Treatment. The calculated MOEs were well above the target MOE of 300. Cancer risk for workers treating cereal seed on-farm was estimated by calculating the LADD. An exposure duration of 10 days was assumed for on-farm treaters. Cancer risk estimates were below 1×10^{-5}. As such, there are no risks of concern for on-farm treating and planting cereal seed with Sedaxane 500FS Fungicide, A17511B Seed Treatment or A16874F Seed Treatment when workers wear the PPE worn in the surrogate study. Given the high MOE and low cancer risk, it was determined that further confirmatory dust off data for wheat, rye and triticale were not required.

Table 5 **Non-cancer risk estimates for workers on-farm treating and planting cereal seeds with Sedaxane 500FS Fungicide, A17511B Seed Treatment or A16874F Seed Treatment**

Worker task	Unit exposure (µg/kg a.i. handled)[1]			Application rate (kg a.i./kg seed)	Seed treated (kg seed/ day)[2]	Exposure (mg/kg bw/day)[3]	Calculated MOE[4]
	Dermal	Inhalation	Total[2]				
On-farm treating and planting (using Dividend study unit exposure values)							
Cereals (barley, wheat, oat, rye and triticale)							
On-farm treating/planting	407.34	223.03	251.54	0.00005	13600	2.44×10^{-3}	7370

[1] For on-farm treating and planting, the arithmetic mean values were used from the Dividend study

[2] Total unit exposure = (Dermal unit exposure × 7% dermal absorption) + Inhalation unit exposure

[3] Exposure = (Total unit exposure × Application rate × Seed treated per day)/(70 kg bw × 1000 µg/mg)

[4] Based on NOAEL = 18 mg /kg bw/day, target MOE = 300

Table 6 **Cancer risk estimates for workers on-farm treating and planting cereal seeds with Sedaxane 500FS Fungicide, A17511B Seed Treatment or A16874F Seed Treatment**

Worker task	ADD (mg/kg bw/day)[1]	Days of exposure	Working Duration (yrs)	LADD (mg/kg bw/day)[2]	Cancer Risk[3]
On-farm treating and planting (using Dividend study unit exposure values)					
Cereals (barley, wheat, oat, rye and triticale)					
On-farm treating/planting	2.44×10^{-3}	10	40	3.57×10^{-5}	1×10^{-7}

[1] ADD = Absorbed daily dose = Exposure from Table 5

[2] LADD = Lifetime average daily dose = $\frac{\text{(ADD} \times \text{Days of exposure} \times \text{Working duration)}}{\text{(365 days/year} \times \text{75 years in lifetime)}}$

[3] Based on $Q_1^* = 3.81\text{x}10^{-3}$ (mg/kg bw/day)$^{-1}$

3.4.3.3 Planting Exposure

Individuals have potential for exposure to Sedaxane 500FS Fungicide, A17511B Seed Treatment and A16874F Seed Treatment while planting treated seed. Chemical specific data for assessing human exposure during planting of treated seed were not submitted. As such, surrogate exposure data have been used to estimate risk to workers planting treated seed.

3.4.3.3.1 Canola and Soybean Seed

Commercially treated canola and soybean seed is bagged. During planting, workers load the treated seeds from bags into the planter. To address planting exposure from bagged canola and soybean seed, the Gaucho planting study was used as a surrogate. In the study, 15 replicates were monitored while planting treated corn seed from bags. The seeds were treated with Gaucho FS 350 or Gaucho FS 600, containing 350 g/L and 600 g/L imidacloprid, respectively. The workers in the study loaded treated seed from bags into the planter and sowed the seed using a closed cab tractor. Dermal exposure for each worker was measured by passive dosimetry using a combination of an inner whole body dosimeter, hand rinses, and face/neck wipes. The inner dosimeter was worn underneath worker clothing. Workers wore a single layer and chemical-resistant gloves. Inhalation exposure was monitored using IOM samplers attached to a personal air sampling pump. The study was of good quality and had only minor limitations. As such, the arithmetic mean values from the study were adequate for risk assessment purposes. The submitted dust off data showed that canola seed treated with Sedaxane 500FS Fungicide + Helix Xtra and soybean seed treated with Sedaxane 500FS Fungicide were both significantly less dusty than Gaucho-treated corn seed (7x less dusty for canola and 28x less for soybean). Therefore, the Gaucho surrogate study is not expected to underestimate planting exposure for canola and soybean seed.

Tables 7 and 8 present the non-cancer and cancer risk estimates, respectively, for the planting exposure for canola and soybean seed treated with Sedaxane 500FS Fungicide. The calculated MOEs were well above the target MOE of 300. Cancer risk for workers planting canola and soybean seed was estimated by calculating the LADD. An exposure duration of 10 days was assumed for planters. Cancer risk estimates were below 1×10^{-5}. Considering the high MOEs and low cancer risk estimates, as well as the difference in dust off of the surrogate study seed and canola and soybean seed, it is expected that the risk from planting Sedaxane 500FS Fungicide-treated canola and soybean seed in open cab tractors is not of concern.

Table 7 Non-cancer risk estimates for workers planting canola and soybean seeds commercially treated with Sedaxane 500FS Fungicide

Worker task	Unit exposure (µg/kg a.i. handled)[1]			Application rate (kg a.i./kg seed)	Seed treated (kg seed/day)	Exposure (mg/kg bw/day)[3]	Calculated MOE[4]
	Dermal	Inhalation	Total[2]				
Planting commercially treated seed (using Zietz 2007 study unit exposure values)							
Canola							
Planting	1515	82.83	188.88	0.00005	600	8.09×10^{-5}	222000
Soybean							
Planting	1515	82.83	188.88	0.00005	20000	2.70×10^{-3}	6670

[1] For planting commercial treated seed, the arithmetic mean values were used from the Gaucho study

[2] Total unit exposure = (Dermal unit exposure × 7% dermal absorption) + Inhalation unit exposure

[3] Exposure = (Total unit exposure × Application rate × Seed treated per day)/(70 kg bw × 1000 µg/mg)

[4] Based on NOAEL = 18 mg /kg bw/day, target MOE = 300

Table 8 Cancer risk estimates for workers planting canola and soybean seeds commercially treated with Sedaxane 500FS Fungicide

Worker task	ADD (mg/kg bw/day)[1]	Days of exposure	Working Duration (yrs)	LADD (mg/kg bw/day)[2]	Cancer Risk[3]
On-farm treating and planting (using Dividend study unit exposure values)					
Canola					
Planting	8.09×10^{-5}	10	40	1.18×10-6	4.51×10^{-9}
Soybean					
Planting	2.70×10^{-3}	10	40	3.94×10^{-5}	1.50×10^{-7}

[1] ADD = Absorbed daily dose = Exposure from Table 7

[2] LADD = Lifetime average daily dose = $\frac{\text{(ADD × Daysof exposure × Working duration)}}{\text{(365 days/year × 75 years in lifetime)}}$

[3] Based on $Q_1^* = 3.81\text{x}10^{-3}$ (mg/kg bw/day)$^{-1}$

3.4.3.3.2 Cereal Seed (Barley, Wheat, Oat, Rye and Triticale)

For cereal seed, the estimates of on-farm treating and planting using the Dividend 36FS study are expected to cover off planting of commercially treated seed, since the same amount is expected to be planted and the transfer of treated seed (bulk transfer into planters) is the same as on-farm planting.

3.4.4 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal when planting treated seed.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

Exposure to residues of the co-active ingredients difenoconazole, metalaxyl-m and thiamethoxam in food and drinking water is not expected to change from existing registered uses of these active ingredients. The use of difenoconazole and metalaxyl-m fits within the registered use pattern for these actives on wheat, barley, triticale, rye and oats. The use of thiamethoxam fits within the registered use pattern for this active on wheat, barley, triticale and rye, but not on oats. Although the use of thiamethoxam on oats is at a rate higher than the maximum rate registered, previously reviewed crop field trial data for thiamethoxam on cereals can support the increase in application rate.

The residue definition (RD) for enforcement and risk assessment in all crops (primary and rotational) is sedaxane. This residue definition applies only to seed treatment applications. Specht (QuEChERS) multiresidue method P-14.141 (LC-MS/MS) is acceptable as the enforcement method for residues of sedaxane, determined as the two isomers SYN508210 (trans) and SYN508211 (cis), in/on crop commodities. The freezer storage stability data indicate that residues of sedaxane, determined as the two isomers SYN508210 and SYN508211, are stable at approximately -18 °C for 24 months in wheat grain, wheat straw, spinach, potato, orange, lentils, and soybeans; residues of the metabolites CSCD667584, CSCD658906, CSCD659089, CSCD668403, CSCD667555, and CSCC210616 are stable at approximately -18 °C for 6 months in wheat grain, wheat straw, spinach leaves, potato tuber, orange (fruit), dried broad beans, and soybean seeds; residues of the metabolite CSCD465008 were stable at approximately -18 °C for 6 months in orange (fruit), dried broad beans, and soybean seeds; residues of the metabolites CSCD465008 and CSAA798670 are stable at approximately -18 °C for 12 months in wheat grain, wheat straw, barley forage, spinach leaves, carrot leaves, and carrot roots; residues of sedaxane, determined as the two isomers SYN508210 and SYN508211, are stable at approximately -20 °C for 6 months in processed commodities of wheat (flour, germ, and bran), soybean (meal, hulls, and oil) and orange (dried pulp, juice, and oil). Submission of the pending results for the metabolite CSCD465008 at 6 and 12 months are required to confirm the stability of CSCD465008 in soybean oil, meal and hulls. The final freezer storage stability study reports for sedaxane metabolites in crop commodities up to 24 months (Report T014683-05-REG), and for sedaxane residues in processed commodities up to 12 months (Report KP-2009-02) are required to support the maximum storage intervals of samples from the magnitude of the residues studies. Residues of sedaxane and metabolites were not detected above the LOQ in the grain or seed, and processed commodities of barley, canola, soybean and wheat. Supervised residue trials conducted throughout the United States and Canada using end-use products containing sedaxane at GAP or at exaggerated rates in or on barley, canola, soybean and wheat are sufficient to support the proposed maximum residue limits (MRLs).

The residue definition in livestock is sedaxane, both for enforcement and risk assessment purposes. Specht (QuEChERs) multiresidue method P-14.141 (LC-MS/MS) is suitable for the enforcement of the two sedaxane isomers SYN508210 and SYN508211 in livestock commodities. GRM023.10A (LC-MS/MS) is suitable for enforcement of the two sedaxane isomers SYN508210 and SYN508211, and the metabolites CSCD658906 and CSCD659087 in livestock commodities. No data are required demonstrating the stability of sedaxane and metabolites during freezer storage given that samples during the dairy cattle feeding study were extracted and analyzed within 30 days. The data from the dairy cattle feeding study indicate that residues of sedaxane, determined as the two isomers SYN508210 and SYN50821, and the metabolites CDCD658906 and CSCD659087 are not expected above the limit of quantitation in the meat, meat by-products and milk as a result of feeding crops treated with sedaxane. Based on the results of the hen metabolism study and the estimated dietary burden, there is no reasonable expectation of finite residues of sedaxane in the meat, meat by-products and eggs of poultry from the uses of sedaxane.

3.5.2 Dietary Risk Assessment

Acute and chronic dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID™, Version 2.14), which uses updated food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The basic chronic analysis assumed 100% crop treated, default processing factors (where available), and the proposed MRLs for all commodities. The basic chronic dietary exposure from all supported sedaxane food uses (alone) for the total population, including infants and children, and all representative population subgroups is $\leq$0.8% of the acceptable daily intake (ADI). Aggregate exposure from food and water is considered acceptable. The PMRA estimates that chronic dietary exposure to sedaxane from food and water is 0.3% (0.000156 mg/kg bw/day) of the ADI for the total population. The highest exposure and risk estimate is for children 1-2 years old at 0.9% (0.000538 mg/kg bw/day) of the ADI. The lifetime cancer risk from the use of sedaxane (food and water) is considered acceptable (5.9×10^{-7}).

3.5.2.2 Acute Dietary Exposure Results and Characterization

The basic acute analysis assumed 100% crop treated, default processing factors (where available), and the proposed MRLs for all commodities. The basic acute dietary exposure for all supported sedaxane food (alone) uses is estimated to be 0.05-0.35% of the ARfD for all subpopulations (95th percentile, deterministic). Aggregate exposure from food and water is considered acceptable: 0.06% to 0.37% of the ARfD. The highest exposure and risk estimate is for children 1-2 years old at 0.37% (0.001122 mg/kg bw/day) of the ARfD.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for sedaxane consists of exposure from food and drinking water sources only as discussed in the previous section.

3.5.4 Maximum Residue Limits

Table 3.5.1 Proposed Maximum Residue Limits

Commodity	Recommended MRL (ppm)
Barley; dry soybeans; oats; rye; rapeseed (canola); triticale; wheat Eggs; fat, meat, and meat byproducts of cattle, goats, hogs, horses, poultry and sheep; milk	0.01

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Based on its physical-chemical properties, sedaxane is soluble in water, is not likely to volatilize from moist soil or water surfaces under field conditions, and is not likely to bioconcentrate or bioaccumulate in organisms. Sedaxane is expected to be stable to photolysis in both terrestrial and aquatic environments. The environmental fate data for sedaxane is summarized in Appendix 1, Table 8.

The most important route of dissipation for sedaxane residues in the terrestrial environment is expected to be adsorption to soil and possibly uptake into growing plants. Sedaxane is expected to be persistent when applied directly to soil, with three major transformation products, CSCC210616, CSCD465008 and CSAA798670, observed under aerobic soil conditions; no major transformation products were formed under anaerobic soil conditions (see Appendix 1, Table 7 for list of all transformation products). When sedaxane is applied to aerobic soil as a seed treatment the apparent half-life is decreased and sedaxane is moderately persistent due to sorption of sedaxane residues to the seed coat and uptake into the sprouting plant.

Due to its persistence in soil, sedaxane has potential to carry over to the next growing season after use. Considering the maximum application rate is low (10.91 g a.i./ha) and its resultant dissipation due to uptake in plant material, sedaxane residues are, however, not expected to carry over in the soil in measureable amounts. Interim results from a 5 year long soil accumulation trial showed no evidence of soil accumulation for sedaxane, CSCC210616, CSCD465008 and CSAA798670. In the case where the application rates were to increase and/or a different application method were used, a new soil accumulation study reflective of the new proposed application rates/methods may be required.

Laboratory studies on adsorption/desorption indicate that sedaxane has potential to be moderately mobile. One of the major biotransformation, CSCD465008, has the potential to be mobile in a variety of soils. CSCD465008 was found to be persistent and very water soluble. No corresponding studies were submitted for the minor transformation products CSAA798670 or CSCC210616, which are assumed to exist as the transformation products preceding CSCD465008 (see soil biotransformation pathway, Appendix 1, Figure 1).

Sedaxane was not found below the soil depth of 10 cm in field studies except in one sample. Measureable amounts of CSCC210616 were found in one instance in the top 10 cm soil layer. Otherwise, no residues of any transformation products were found. However, the soils were not analysed below the 30 cm soil depth. The leaching potential of sedaxane in the field is most probably offset by its adsorption to soil particles, therefore, the potential for groundwater contamination is expected to be limited.

Hydrolysis and biotransformation in aquatic systems are not expected to be important routes of transformation for sedaxane. Sedaxane is stable to hydrolysis, and although it can undergo photolysis in the aquatic environment, laboratory studies show it to be persistent in water/sediment systems. Three major transformation products were identified in photolysis studies. As sedaxane is incorporated into the soil when used as a seed treatment, the potential for sedaxane to enter the aquatic environment through runoff is expected to be limited.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (i.e. protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC = 1). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

Risk of sedaxane to terrestrial organisms was based upon evaluation of toxicity data for the following (see Appendix 1, Tables 9 and 10):

- 1 mammal species (acute oral and long term (reproduction) dietary exposure)
- 3 bird species (acute oral exposure, short- and long term (reproduction) dietary exposure)
- One bee species, four other arthropods and one earthworm species representing invertebrates (acute and long term exposure with technical grade active ingredient and end-use products)
- Ten crop species representing non-target plants

Earthworms and soil-dwelling arthropods
Sedaxane is not acutely toxic to earthworms up to the highest concentration tested (up to 1000 mg a.i./kg soil). The representative formulation of sedaxane, A16148F, did not adversely affect the fecundity of soil mites (*Hypoaspis aculeifer*) or the rove beetle (*Aleochara bilineata*) in any treatment groups up to 225 g A16148F/ha (137 µg sedaxane/kg dry soil). The screening level risk assessment was determined based on the EECs for the highest use rate scenario for sedaxane on triticale (10.91 g a.i./ha). The level of concern (LOC) was not exceeded for earthworms, soil mites or rove beetles (Appendix I, Table 9).

Bees (pollinators) and beneficial arthropods
Sedaxane was considered relatively non-toxic to bees on a contact basis. An acute oral toxicity test submitted for bees was determined to be not scientifically valid. Given that sedexane is not systemic, and as sedaxane is incorporated into the soil when used as a seed treatment the potential oral exposure of pollinators via pollen and nectar and contact exposures of beneficial arthropods are expected to be very limited. At this time additional studies on acute oral toxicity for bees are not being requested. Additional studies maybe required in the future if there are changes to the use pattern or application method.

A number of toxicity studies were submitted for beneficial insects using the representative formulation, A16148F. Effects on mortality and reproduction of the parasitoid wasp (*Aphidius rhopalosiphi*) were observed at 24.6 mL A16148F/ha. No significant effects on reproductive capacity were seen at rates up to 320 mL/ha for the predatory mite (*Typhlodromus pyri*).

Non-Target Plants
Very limited exposure to non-target terrestrial plants is expected due to the use of sedaxane as a seed treatment. Toxicity to non-target terrestrial plants was determined based on the review of a seedling emergence test in which no effects were noted in ten representative crop species at the highest application rate of 107 g a.i./ha using the A16148F seed treatment.

Birds and small wild mammals
No treatment related mortalities or clinical effects were observed in the acute oral and dietary exposure of sedaxane to various bird species including Northern bobwhite quail (*Colinus virginianus*), mallard duck (*Anas platyrhynchos*), and canary (*Serinus canaria*).

There was a slight, but significant ($p<0.05$) adverse effect on Northern bobwhite reproduction (eggs cracked, ratio of number hatched to live 3-week embryos) at the highest treatment level tested.

No treatment-related effects were observed on the reproduction for mallard ducks (*Anas platyrhynchos*) although low egg productivity in the control groups resulted in control values being lower than the treatment groups for all egg production-related endpoints (i.e. eggs laid, eggs set, viable embryos, live 3-week embryos, number hatched, and 14-day survivors).

No treatment related mortalities were observed in acute oral exposure to rats. No treatment related effects were observed for rats in a two-generation reproductive study.

No mortality was observed during acute oral exposure of sedaxane to rats. A significant reduction in litter size was observed in the two-generation reproduction study.

The screening level risk assessment was performed with triticale as the surrogate seed type. The estimated dietary exposures and the toxicity endpoints were both expressed as the number of seeds consumed per day. The LOC was not exceeded for birds or mammals of any body weight for acute, dietary or reproductive exposures.The results of the risk assessment are presented in Appendix I, Table 10.

4.2.2 Risks to Aquatic Organisms

Risk of sedaxane to freshwater aquatic organisms was based upon the evaluation of toxicity data for the following:

- one invertebrate species; daphnid (acute and long term exposure)
- three fish species (acute and chronic)
- four algae species and one vascular plant species

Risk of sedaxane to marine aquatic organisms was based upon the evaluation of toxicity data for the following:

- one fish species (acute exposure)
- two invertebrate species (acute exposure); mysid (acute exposure) and mollusk (acute exposure)
- one algae species (acute exposure)

A summary of the freshwater and marine/estuarine toxicity data for sedaxane is presented in Appendix I, Table 11. For the assessment of risk, toxicity endpoints from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed to sedaxane.

The potential for over-land run-off of sedaxane to the aquatic environment is limited based on its use as a seed treatment. Nevertheless, the potential for adverse effects on aquatic organisms was assessed based on EECs using the equivalent input from the direct application of the seed treatment rate of sedaxane (10.91 g a.i./ha) to water. The result of the screening level risk assessment for aquatic organisms is presented in Appendix I, Table 11.

Aquatic Invertebrates

Sedaxane was not acutely toxic to freshwater aquatic invertebrates (*Daphnia magna*) and the only sublethal effect noted was immobility. Immobility was also observed in the acute toxicity test conducted on *Daphnia magna* with the transformation product CSCD465008.

The screening level risk assessment did not identify potential risks to freshwater aquatic species (Appendix I, Table 11).

Freshwater Fish

The toxicity of sedaxane to rainbow trout and common carp were used to assess potential for acute effects while potential effects from chronic exposure were assessed using results from studies on fathead minnow.

The screening level risk assessment was performed with the common carp (acute) and fathead minnow (chronic). The LOC to exposure to sedaxane was not exceeded for either the acute or chronic exposure scenarios (Appendix I, Table 11).

In an acute toxicity test of the transformation product CSCD465008 to rainbow trout (*Oncorhynchus mykiss*) some mortality was observed relative to the control group although no sub-lethal effects were observed and no risks were identified

Using toxicity endpoints for the most sensitive fish species with a 0.1 uncertainty factor as a surrogate for amphibians toxicity, potential effects on survival and reproduction were assessed. No potential risks to amphibians were identified in the screening level risk assessment.

Freshwater algae and vascular plants
Toxicity tests for sedaxane were performed on a variety of freshwater algae: the cyanobacterium *Anabaena flos-aquae,* the diatom algal species *Navicula pelliculosa,* the green alga *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*). No adverse effects were observed at any test level for *Anabaena flos-aquae* but inhibition as high as 98% in cell density was observed for *Navicula pelliculosa*. Significant inhibitory effects on the biomass, yield, growth rate, and cell density of *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*) were observed after 96 hours at concentrations of 2.2 mg a.i./L and greater. *Lemna gibba* showed growth inhibition upon exposure to sedaxane ranging from 8–84%, and the most sensitive endpoint was found to be dry weight. There were no morphological abnormalities in the control or three lowest test levels. In the remaining treatment groups, the fronds were smaller and yellow or brown as compared to the control. Furthermore, the roots were shorter and newly formed fronds were stunted at the two highest test levels.

The LOC was not exceeded in screening level assessment for any freshwater algae or vascular plants (Appendix I, Table 11).

Marine/estuarine species
Sedaxane was acutely toxic to mysid shrimp (*Mysidopsis bahai*) and this species was found to be the most sensitive marine invertebrate. Sublethal effects were noted in acute toxicity tests conducted on the eastern oyster, *Crassostrea virginica* (effects on shell growth), the sheepshead minnow, *Cyprinodon variegatus,*(lethargy, loss of equilibrium), the marine diatom *Skeletonema costatum* (inhibition of cell densities).

No sublethal effects were noted in an acute toxicity test conducted with CSCD465008 on *Pseudokirchneriella subcapitata*.

The screening level risk assessment did not identify potential risks to marine/estuarine aquatic species (Appendix I, Table 11).

5.0 Value

5.1 Effectiveness Against Pests

5.1.1.1 Efficacy claims for Sedaxane 500FS Fungicide

5.1.1.1.1 Control of seed decay, seedling blight and damping-off caused *Rhizoctonia solani* on barley, wheat, oats, rye, and triticale

A total of five trials conducted on wheat were provided where the efficacy of Sedaxane 500FS Fungicide against seed and seedling diseases caused by *Rhizoctonia* was tested. The trials were inoculated to ensure adequate disease pressure and pathogen identity. The product was shown to be effective in significantly increasing the number of emerging seedlings relative to untreated disease-inoculated seeds as well as maintaining stand counts and seedling health after emerging from the soil. Based on this demonstrated efficacy, a claim for control of *Rhizoctonia* causing seed decay, seedling blight, root rot and damping-off is accepted for the Sedaxane 500FS Fungicide label. Extension of this claim to include all other cereals was deemed acceptable on the basis that their seeds are very similar in terms of size and biology.

5.1.1.1.2 Control of seed decay, seedling blight and damping-off caused Rhizoctonia solani on canola

Evidence to support this claim for use on canola was presented in the form of six trials conducted in Canada where Sedaxane 500FS Fungicide was applied alone to seeds inoculated with *Rhizoctonia*. Sedaxane provided protection at all stages of seedling development where significant increases were shown in the number of emerging seedlings relative to untreated disease-inoculated seed. In addition, significant increases in fresh weights of young plants were used as indirect support for claims of improved seedling health. Based on these findings along with sedaxane efficacy demonstrated against these diseases in other crop seedlings, the claim for use on canola was deemed acceptable for inclusion on the Sedaxane 500FS Fungicide label.

5.1.1.1.3 Control of seed decay, seedling blight and damping-off caused *Rhizoctonia solani* on soybeans

Evidence to support this claim for use on soybean was presented in the form of six trials conducted in Canada where Sedaxane 500FS Fungicide was applied to soybean seeds inoculated with *Rhizoctonia*. Sedaxane provided protection at all stages of seedling development where significant increases were shown in the number of emerging seedlings relative to untreated disease-inoculated seed. In addition, direct assessments of seedling blight showed significant reductions in disease severity in a number of different instances under high disease pressure. Based on these findings, this claim for use on soybean was deemed acceptable for inclusion on the Sedaxane 500FS Fungicide label.

5.1.1.1.4 Control of loose smut on wheat and barley

Across seven trials conducted on barley, average levels of 97% and 99% control of loose smut, relative to untreated seeds, were observed on barley seeds treated with the low and high rates of sedaxane, respectively. Efficacy of sedaxane against loose smut in wheat was demonstrated in an additional two trials where disease was completely controlled by the lower rate of the active ingredient, 2.5 g/ha.

5.1.1.2 Efficacy claims for the pre-mixed products A17511B Seed Treatment and A16874F Seed Treatment

5.1.1.2.1 Control claims supported by efficacy demonstrated for Sedaxane 500FS Fungicide

Seven trials conducted on barley were submitted to demonstrate that loose smut control by the active ingredient sedaxane was not impacted by the presence of the other active ingredients found in the pre-mixed products A17511B Seed Treatment and A16874F Seed Treatment. Although these trials were conducted on loose smut of barley, there is no reason to expect that this finding does not apply to seed and seedling diseases of different crops caused by other pathogens where sedaxane was shown to be effective.

Based on this information, claims deemed acceptable for the Sedaxane 500 FS Fungicide label were accepted in support of the following control claims on both sedaxane-containing pre-mixed products: a) seedling blight, root rot, and damping-off in cereals caused by pathogens in the genus *Rhizoctonia*; b) loose smut on barley and wheat. The latter claim was extended to include all other cereals on the labels of the pre-mixed products based on similarities in sizes and biology of their seed.

5.1.1.2.2 Control and suppression claims supported by precedent registrations

Based on previously registered claims for the same diseases on other products containing only metalaxyl-m and difenoconazole, the following claims were supported for inclusion on the A17511B Seed Treatment and A16874F Seed Treatment labels:

- Control of general seed rots on cereals
- Control of seedling blight, root rot, and damping-off caused by *Fusarium*, and *Pythium* on cereals
- Control of seed-borne septoria on barley, rye and winter wheat
- Control of covered smut on barley and oats
- Control of false loose smut on barley
- Control of common bunt and dwarf bunt on rye and wheat
- Control of early season septoria leaf blotch on winter wheat
- Suppression of common root rot on cereals
- Suppression of crown and foot rot on barley, rye, triticale, and wheat
- Suppression of take-all on barley, rye, triticale, and wheat

The use directions on the registered products result in equivalent rates of all fungicidal active ingredients with the exception of sedaxane. There was no evidence to indicate a possible reduction in efficacy of metalaxyl-m and difenoconazole when sedaxane is included in a pre-mixed formulation. These claims all provide value by broadening the potential range of pathogens targeted by single applications of either A17511B Seed Treatment or A16874F Seed Treatment.

5.1.1.3 Control or suppression of wireworm on cereals

The claim for suppression/control of wireworm on barley, oats, rye, triticale and wheat was supported for inclusion on the A17511B Seed Treatment label based on the registered use pattern for thiamethoxam, difenoconazole and metalaxyl-m. No loss of insecticidal activity was expected with the addition of the fungicide sedaxane. Use claims were extrapolated to oats based on the similarity in seed sizes between barley, wheat and oats.

5.1.1.4 Tank mix claims

Various recommendations for tank-mixes with other products (fungicides and insecticides) were supported for inclusion on each of the sedaxane end-use products. All of the tank mixes were deemed acceptable as these were determined to be congruent with currently registered use directions on the tank-mix partner labels. Additionally, each of the tank mixes provided the benefit of either introducing a new mode of action in the management of a given pest or of increasing the potential range of pest protection from a single application.

5.2 Phytotoxicity

No crop injury attributable to applications of sedaxane products as seed treatments was reported in any of the efficacy trials.

5.3 Economics

No market analysis was done for this application.

5.4 Sustainability

5.4.1 Survey of Alternatives

The fungicidal active ingredients listed in Appendix I, Table 13 are found in products that are registered for control or suppression of diseases indicated on the labels for Sedaxane 500FS Fungicide, A17511B Seed Treatment and A16874F Seed Treatment.

5.4.2 Compatibility with Current Management Practices Including Integrated Pest Management

Recommended applications of Sedaxane 500FS Fungicide, A17511B Seed Treatment and A16874F Seed Treatment on labelled crops are not expected to interfere with any preventative measures employed to reduce disease pressure including IPM strategies.

5.4.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Sedaxane is a member of the SDHI fungicide class (FRAC group 7 carboxamides). No cross resistance to any compound of a different fungicide class is expected but within the same fungicide class, cross-resistance may occur. SDHI fungicides are currently classified as bearing medium to high risk of disease resistance development by FRAC. In cases where pathogens with medium to high resistance risks are concerned, it is recommended that sedaxane alone is used in mixtures with an appropriate partner that is active in its own right against current field populations of the target pathogen at the applied dose. However, solo treatments of sedaxane can be used in cases where pathogens with low resistance risk are concerned such as *Rhizoctonia* and loose smut. FRAC has not reported resistance to any of the labelled diseases.

5.4.4 Contribution to Risk Reduction and Sustainability

The use of Sedaxane 500FS Fungicide, A17511B Seed Treatment and A16874F Seed Treatment fits well into IPM programs. Since sedaxane is for use in seed treatments, the amount of product that will be applied is small relative to other methods of application such as ground or foliar sprays. Sedaxane provides an effective management tool for seed and soil-borne diseases of significant economic impact to major crops in Canadian agriculture.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e., persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, sedaxane and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[4] and evaluated against the Track 1 criteria (Appendix 1, Table 12). The PMRA has concluded Sedaxane does not meet all Track 1 criteria, and is not considered a Track 1 substance.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical and formulants and contaminants in the end-use products are compared against the *List of Pest control Product Formulants and Contaminants of Health or Environmental Concern* maintained in the *Canada Gazette*.[5] The list is used as described in the PMRA Notice of Intent NOI2005-01[6] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02,[7] and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

> The end-use products, A17511B, A16874F and A16148C Seed Treatments contain a formulant which has low level contamination with chlorinated dioxin and furan Track 1 contaminants which are identified in the *Canada Gazette*. The PMRA is managing the presence of these contaminants in accordance with the Agency's strategy to prevent or minimize releases, with the ultimate goal of virtual elimination as described in DIR99-03. The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Summary

7.1 Human Health and Safety

The toxicology database submitted for sedaxane is comprehensive. The scientific quality of the data is high and the database is considered adequate to define the majority of the toxic effects that may result from exposure to sedaxane. A short-term inhalation toxicity study and ovarian follicle counts at the low and mid dose levels in a 2-generation reproductive toxicity study were not provided, and are being required as conditions of registration. There was no evidence of increased susceptibility of the young in reproduction or developmental toxicity studies. Sedaxane did not cause immunosuppression in mice. There was evidence of neurotoxicity at high doses in rats. In short-term and long-term studies on laboratory animals, the primary targets were the liver, endocrine organs and circulatory system. There was no evidence that sedaxane was genotoxic; however, there was evidence of oncogenicity in mice and rats after chronic dosing. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

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[4] DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy.

[5] *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* and in the order amending this list in the *Canada Gazette*, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. *Part 1 Formulants of Health or Environmental Concern, Part 2 Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions and Part 3 Contaminants of Health or Environmental Concern.*

[6] NOI2005-01, List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern under the New Pest Control Products Act.

[7] DIR2006-02, Formulants Policy and Implementation Guidance Document.

The nature of the residue in plants and animals is adequately understood. The residue definition (RD) for enforcement and risk assessment in all crops (primary and rotational) and animals is sedaxane. The use of sedaxane on crops listed on the labels do not constitute an unacceptable chronic or acute dietary risk (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend maximum residue limits. The PMRA recommends that the following maximum residue limits be specified for sedaxane:

Commodity	Recommended MRL (ppm)
Barley; dry soybeans; oats; rye; rapeseed (canola); triticale; wheat Eggs; fat, meat, and meat byproducts of cattle, goats, hogs, horses, poultry and sheep; milk	0.01

Workers treating seed with Sedaxane 500FS Fungicide, A17511B Seed Treatment or A16874F Seed Treatment and workers planting treated seed are not expected to be exposed to levels of sedaxane that will result in an unacceptable risk when Sedaxane 500FS, A17511B and A16874F are used according to label directions. The personal protective equipment on the product label is adequate to protect workers.

7.2 Environmental Risk

No unacceptable environmental risks are anticipated from the proposed use of sedaxane as a seed treatment.

Label revisions were required for A16874F and A16148B Seed Treatments as they contain additional active ingredients. This will maintain consistency with labels across products. Label statements are being required to inform users of risk to birds and mammals in order to help minimize risk from ingestion of treated seed. The end-use product A17511B Seed contains sedaxane, difenoconazole, metalaxyl-m, and thiamethoxam and A16874F Seed treatment contains sedaxane, difenoconazole, metalaxyl-m. As A17511B Seed treatment includes the neonicotinoid insecticide, thiamethoxam, a hazard statement specific to pollinators was also added to maintain consistency with other registered seed treatment products containing thiamethoxam (for example, Cruiser Maxx Cereals Seed Treatment Registration Number 29192 for use on cereal crops).

7.3 Value

The rationales based on precedent claims and data submitted to register Sedaxane 500FS Fungicide, A17511B Seed Treatment and A16874F Seed Treatment were sufficient in supporting the value of the products' uses for control or suppression of certain seed and soil-borne diseases and insects in cereals, canola and soybean.

8.0 Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, has granted conditional registration for the sale and use of Sedaxane Technical and A17511B Seed Treatment, containing sedaxane, difenconazole, metalaxyl-m and thiamethoxam, A16874F Seed Treatment, containing sedaxane, difenconazole and metalaxyl-m, and Sedaxane 500FS Fungicide, containing the technical grade active ingredient sedaxane, for use on seed from various crops including certain cereals (barley, wheat, oats, rye, and triticale), canola, and soybean to control or suppress soil and seed-borne diseases of seedlings and mature plants. A17511B Seed Treatment also contains an insecticide to suppress/control wireworm activity on certain cereal crops.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

Although the risks and value have been found acceptable when all risk-reduction measures are followed, as a condition of these registrations, additional scientific information is being requested from the applicant. For more details, refer to the Section 12 Notice associated with these conditional registrations. The applicant will be required to submit this information within the time frames indicated below.

NOTE: The PMRA will publish a consultation document at the time when there is a proposed decision on applications to convert these conditional registrations to full registrations or on applications to renew the conditional registrations, whichever occurs first.

Human Health

- DACO 4.3.6 – Short-term inhalation toxicity study in rats.
- DACO 4.5.1, 4.8 – Low and mid dose assessments of ovarian follicle counts in the 2-generation reproductive toxicity study in rats.
- The final freezer storage stability study reports for sedaxane metabolites in crop commodities up to 24 months (Report T014683-05-REG), and for sedaxane residues in processed commodities up to 12 months (Report KP-2009-02) are required to support the maximum storage intervals of samples from the magnitude of the residues studies.

List of Abbreviations

♂	male
♀	female
µg	micrograms
AD	administered dose
ADD	absorbed daily dose
ADI	acceptable daily intake
ads	adsorption
AFC	antigen forming cells
a.i.	active ingredient
ALT	alanine transaminase
AOPWIN	Atmospheric Oxidation Program
AR	applied radioactivity
ARfD	acute reference dose
AST	aspartate aminotransferase
AUC	area under the curve
BAF	bioaccumulation factor
BBCH	Biologische Bundesanstalt, Bundessortenamt and Chemical Industry
BCF	bioconcentration factor
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
C.I.	confidence interval
cm	centimetres
C_{max}	plasma peak concentration
CO_2	carbon dioxide
CV	coefficient of variation
CYP	cytochrome P450 enzyme (alphanumeric suffixes denote families and sub-families
d	day(s)
DAP	days after planting
DAT	days after treatment
des	desorption
DT_{50}	dissipation time 50% (the dose required to observe a 50% decline in concentration)
DT_{90}	dissipation time 90% (the dose required to observe a 90% decline in concentration)
dw	dry weight
EC_{25}	effective concentration on 25% of the population
EC_{50}	effective concentration on 50% of the population
EEC	estimated environmental concentration
EP	end-use product
EROD	ethoxyresorufin-O-dealkylase
F_1	first generation

fc	food consumption
fe	food efficiency
FRAC	Fungicide Resistance Action Committee
g	gram
GAP	good agricultural practices
GD	gestation day
GUS	groundwater ubiquity score
h	hour(s)
ha	hectare(s)
HAFT	highest average field trial
HDPE	high density polyethylene
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
IgM	immunoglobulin M
IOM	Institute of Occupational Medicine
IPM	Integrated Pest Management
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{FOC}	soil sorption constant normalised for organic carbon
K_{ow}	*n*–octanol-water partition coefficient
L	litre
LADD	lifetime average daily dose
LC_{50}	lethal concentration 50%
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LD	lactation day
LD_{50}	lethal dose 50%
LLMV	lowest level of method validation
LOAEL	lowest observed adverse effect level
LOAEC	low observed adverse effect concentration
LOC	level of concern
LOQ	limit of quantitation
m	metre(s)
MAS	maximum average score
mg	milligram
MIS	maximum irritation score
mL	millilitre
MOE	margin of exposure
MRL	maximum residue limit
MRM	multiresidue methods
MTD	maximum tolerated dose
NAFTA	North American Free Trade Agreement
NIOSH	National Institute for Occupational Safety and Health
nm	nanometre(s)
NOAEL	no observed adverse effect level
NOAEC	no observed adverse effect concentration
NOER	no observed effect rate
NZW	New Zealand white
OVS	OSHA Versatile Sampler

P	parental generation
Pa	pascal
PAMI	Pesticide Analytical Manual Volume I
PBI	plantback interval
PHI	preharvest interval
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
POD	point of departure
PPE	personal protective equipment
ppm	parts per million
Q_1*	cancer potency factor
QA	quality assurance
QC	quality control
QuEChERS	Quick, Easy, Cheap, Effective, Rugged and Safe
RD	residue definition
RPT	rumen-protected tryptophan
RQ	risk quotient
SDHI	succinate dehydrogenase inhibitor
SFO	single first order
SI	stimulation index
TG	triglyceride
TGAI	technical grade active ingredient
T_{max}	time of maximum concentration
TRR	total radioactive residue
TSMP	Toxic Substances Management Policy
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v.p.	vapour pressure
v/v	volume per volume dilution
wt	weight

Appendix I Tables and Figures

Table 1 Residue Analysis

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Plant	Specht (QuEChERS) Multriresidue Method P-14.141	trans (SYN508210) and cis (SYN508211) isomers of sedaxane (SYN524464)[a]	LC-MS/MS (enforcement)	0.05 ppm per analyte	1897777 PMRA Document Number: 1897771 PMRA Document Number: 1897769
	GRM023.01A GRM023.01B (re-write of GRM023.01A) GRM023.03A	SYN508210 SYN508211 CSCD667584 CSCD658906 CSCD659089 CSCD668403 CSCD667555[b] CSCD465008 CSCC210616	LC-MS/MS (data gathering)	0.05 ppm per sedaxane isomer (GRM023.01A and GRM023.01B); 0.01 ppm per metabolite (GRM023.03A)	1897776 PMRA Document Number: 1897783 PMRA Document Number: 1897782 PMRA Document Number: 1897781 PMRA Document Number: 1897774 PMRA Document Number: 1897786
	GRM023.11A	SYN508210 SYN508211 CDCD659089 CSCD668403 CSCD659087 CSAA798670 CSCD465008	LC-MS/MS (data gathering)	0.05 ppm per sedaxane isomer; 0.01 ppm per metabolite	1897773 PMRA Document Number: 1897779 PMRA Document Number: 1897976

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
	GRM023.12A	CSCD465008	LC-MS/MS (data gathering and enforcement)	0.01	1897790 PMRA Document Number: 1897778 PMRA Document Number: 1897787 PMRA Document Number: 1897786
	GRM006.08A	CSCD465008 CSAA798670	LC-MS/MS (data gathering)	0.01	1897784
Livestock	Specht (QuEChERS) Multiresidue Method P-14.141	SYN508210 SYN508211	LC-MS/MS (enforcement)	0.05 ppm per sedaxane isomer	1897777 PMRA Document Number: 1897772 PMRA Document Number: 1897785
	GRM023.10A	SYN508210 SYN508211 CSCD658906 CSCD659087	LC-MS/MS (enforcement)	0.05 ppm per sedaxane isomer; 0.01 ppm per metabolite	1897780 PMRA Document Number: 1897770 PMRA Document Number: 1897788 PMRA Document Number: 1897937
Soil	GRM023.02A	SYN508210	HPLC-MS/MS 330 → 131 m/z	0.0001 mg/kg	1897801, 1897803, 1897791
		SYN508211	330 → 131 m/z		
	GRM023.04A	CSCC210616	HPLC-MS/MS 176 → 156 m/z		1897798, 1897794, 1897806
	GRM023.05A	CSCD465008	HPLC-MS/MS 161 → 141 m/z	0.0005 mg/kg	1897796, 1897792
		CSAA798670	175 → 91 m/z		

Matrix	Method ID	Analyte	Method Type	LOQ	Reference
Sediment	Extended from soil				
Water	GRM023.06A	SYN508210	HPLC-MS/MS 330 → 131 m/z	0.05 µg/L	1897912, 1897809
		SYN508211	330 → 131 m/z		
		CSCC210616	176 → 136 m/z		
		CSCD465008	161 → 141 m/z		
		CSAA798670	175 → 91 m/z		

[a] Technical sedaxane is a mixture of trans and cis isomers, SYN 508210 and SYN508211, in the ratio of ~6:1.

[b] Total CSCD667555 includes contribution from the N-malonyl conjugate (CSCD667556) which is hydrolyzed to the N-glucoside (CSCD667555) under mild basic conditions.

Table 2 Toxicity Profile of End-use Product(s) Containing Sedaxane

(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons)

Study Type/Animal/PMRA #	Study Results
A17511B Seed Treatment	
Acute oral toxicity Sprague-Dawley rats PMRA #1898269	Female LD_{50} > 5000 mg/kg bw Low toxicity
Acute dermal toxicity Sprague-Dawley rats PMRA #1898270	LD_{50} > 5050 mg/kg bw Low toxicity
Acute inhalation toxicity (nose-only) Sprague-Dawley rats PMRA #1898271	LC_{50} > 2.59 mg/L Low toxicity

Study Type/Animal/PMRA #	Study Results
Dermal irritation NZW rabbits PMRA #1898272	MAS = 0, MIS = 0 Non-irritating
Eye irritation NZW rabbits PMRA #1898273	MAS = 1.7, MIS = 6 Minimally irritating
Dermal sensitization (Buehler) Hartley guinea pigs PMRA #1898274	Non-sensitizer
A16874F Seed Treatment	
Acute oral toxicity Sprague-Dawley rats PMRA #1898326	Female LD_{50} > 5000 mg/kg bw Low toxicity
Acute dermal toxicity Sprague-Dawley rats PMRA #1898328	LD_{50} > 5050 mg/kg bw Low toxicity
Acute inhalation toxicity (nose-only) Sprague-Dawley rats PMRA #1898330	LC_{50} > 2.63 mg/L Low toxicity

Study Type/Animal/PMRA #	Study Results
Dermal irritation NZW rabbits PMRA #1898332	MAS = 0, MIS = 0 Non-irritating
Eye irritation NZW rabbits PMRA #1898333	MAS = 1.7, MIS = 11 Minimally irritating
Dermal sensitization (Buehler) Hartley guinea pigs PMRA #1898334	Non-sensitizer
Sedaxane 500FS Fungicide	
Acute oral toxicity Sprague-Dawley rats PMRA #1898367	Female LD_{50} = 2975 mg/kg bw (95% C.I. 844->20 000 mg/kg bw) Low toxicity
Acute dermal toxicity Sprague-Dawley rats PMRA #1898368	LD_{50} > 5050 mg/kg bw Low toxicity
Acute inhalation toxicity (nose-only) Sprague-Dawley rats PMRA #1898369	LC_{50} > 2.56 mg/L Low toxicity

Study Type/Animal/PMRA #	Study Results
Dermal irritation NZW rabbits PMRA #1898370	MAS = 0, MIS = 0.67 Non-irritating
Eye irritation NZW rabbits PMRA #1898371	MAS = 1.3 Minimally irritating
Dermal sensitization (Buehler) Hartley guinea pigs PMRA #1898372	Non-sensitizer

Table 3 **Toxicity Profile of Technical Sedaxane**
(Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Organ weight effects reflect both absolute organ weights and relative organ to bodyweights unless otherwise noted)

Study Type/Animal/PMRA #	Study Results
Acute oral toxicity Wistar rats PMRA #1897844	Female LD_{50} = 5000 mg/kg bw (95% C.I. 2513-9210 mg/kg bw) Low toxicity
Acute dermal toxicity Wistar rats PMRA #1897848	LD_{50} > 5000 mg/kg bw Low toxicity
Acute inhalation toxicity (nose-only) Wistar rats PMRA #1897850	LC_{50} > 5.244 mg/L Low toxicity

Study Type/Animal/PMRA #	Study Results
Dermal irritation NZW rabbits PMRA #1897853	MAS = 0, MIS = 0 Non-irritating
Eye irritation NZW rabbits PMRA #1897856	MAS = 0.89 Minimally irritating
Dermal sensitization (LLNA) CBA/CaBkl mice PMRA #1897858	SI < 3 Non-sensitizer
Metabolism/Toxicokinetics - single and repeated dose, oral gavage Wistar rats PMRA #1897819, 1897822, 1897824, 1897827, 1897829, 1897832, 1897834	**Absorption:** Sedaxane was rapidly and extensively absorbed (>87% of total recovered radioactivity). Maximum plasma concentrations of total radioactivity were achieved at 1-6 h post dose and declined with estimated terminal half-life values ranging from 23-29 hours. Similar terminal half-life values of 21-40 hours were obtained for blood. At both dose levels, systemic exposure was similar for males and females. **Distribution:** Tissue distribution of radiolabelled sedaxane was extensive in rats. Tissue concentrations were highest in the liver, kidney and fat. With repeated dosing, small increases in concentration occurred at these sites and in the spleen. Following the cessation of dosing, all tissue concentrations declined, with no evidence of any persistence. There were no pronounced sex differences in tissue distribution or depletion profiles between the sexes or following single or repeated doses. **Metabolism:** Sedaxane was extensively metabolized via demethylation, hydroxylation, oxidation and conjugation affording an array of hydroxylated metabolites and metabolites formed by cleavage of the terminal cyclopropyl moiety. An equivalent range of metabolites of desmethyl sedaxane was also formed. The major fecal/biliary metabolites were identified as trans para phenol and desmethyl trans para phenol metabolites, which together with the equivalent cis para phenol isomers accounted for approximately half of the administered dose (AD). Low levels (<1% AD) of a pyrazole amide metabolite were also detected in bile samples. The phenolic and hydroxy metabolites of sedaxane and desmethyl sedaxane were subject to glucuronic acid, sulphate and glutathione conjugation. Unchanged parent represented less than 10% AD in excreta. There were no major sex or dose related differences apparent in the qualitative metabolite profile for sedaxane. **Excretion:** The routes and rates of excretion were similar in male and female rats and at both dose levels. Over 2 days post dosing, males and females excreted >93% AD. The major route of excretion was via the feces/bile (79-88% AD), while urinary excretion accounted for 12-19% AD. Elimination of sedaxane via respired volatiles or CO_2 was negligible. There were no apparent differences in excretion between the sexes, between the dose levels or after repeated dosing.

Study Type/Animal/PMRA #	Study Results
28-day dermal Wistar rats PMRA #1897885	NOAEL = 1000 mg/kg bw/day LOAEL not established
90-day inhalation PMRA #1943343	The waiver request was not granted. Criteria for low acute toxicity (US EPA Category IV) and low volatility were met; however, based on the expected inhalation scenarios for sedaxane EPs, this risk is not considered to be adequately characterized via the available repeat-dose oral toxicity studies.
28-day dietary (supplemental) CD-1 mice PMRA #1897863	Effect levels were not established since this was a range-finding supplemental study. No treatment-related effects were observed.
28-day capsule (supplemental) Beagle dogs PMRA #1897860	Effect levels were not established since this was a range-finding supplemental study. At ≥100 mg/kg bw/day, ↑ hepatocellular vacuolation (♀) At 300 mg/kg bw/day, ↑ liver weight, enlarged liver, hepatocellular hypertrophy and vacuolation (♂); ↓ bwg, fc, cholesterol, phospholipid (♀)
90-day dietary CD-1 mice PMRA #1897869	NOAEL = 567/1167 mg/kg bw/day ♂/♀ LOAEL = 1455/not established mg/kg bw/day (♂/♀), based on ↓ bw, bwg, fc, total bilirubin; ↑ adjusted liver and testes weights (♂). No treatment-related effects in females.
90-day dietary toxicity Wistar rats PMRA #1897866	NOAEL = 72.9/85.7 mg/kg bw/day ♂/♀ LOAEL = 299.6/315.3 mg/kg bw/day ♂/♀, based on ↓ bw, ↓ fc, ↓ fc, ↑ centrilobular hypertrophy, ↑ pigmentation in the liver, ↑ TG, ↑ total protein, ↑ liver weight; ↑ prothrombin time, ↑ plasma albumin (♂); ↑ platelet counts, ↑ cholesterol, ↓ heart wt (♀)
90-day dietary toxicity Wistar rats PMRA #1897873	NOAEL = 24.8/28.3 mg/kg bw/day ♂/♀ LOAEL = 168.0/186.0 mg/kg bw/day ♂/♀, based on ↓ forelimb grip strength; ↓ bw, ↓ bwg, ↓ fc, ↓ hindlimb grip strength (♀)
90-day capsule Beagle dogs PMRA #1897878	NOAEL = 150/not established ♂/♀ LOAEL = 400/50 mg/kg bw/day ♂/♀, based on ↓ bw, ↓ bwg, ↓ lymphocyte count, ↓ cholesterol, ↓ spleen weights (♂); ↓ bw, ↓ bwg (♀)
12-month capsule Beagle dogs PMRA #1897881	NOAEL = 50 mg/kg bw/day LOAEL = 200 mg/kg bw/day, based on ↓ bw, ↓ bwg, ↓ fc, ↓ cholesterol, ↓ spleen weights, ↓ testes weight

Study Type/Animal/PMRA #	Study Results
80-week dietary CD-1 mice PMRA #1897905	NOAEL = 157/185 mg/kg bw/day ♂/♀ LOAEL = 900/1001 mg/kg bw/day ♂/♀, based on ↓ bw, ↓ bwg , ↓ fc; ↑ liver weight, ↑ hepatocellular adenomas, carcinomas and combined hepatocellular adenomas and carcinomas (♂); ↓ bw, ↓ bwg , ↓ fc (♀) **Evidence of oncogenicity in males at a dose that approached the limit dose (900 mg/kg bw/day). Dosing was considered adequate.**
104/105-week dietary (with 53-week chronic toxicity) Wistar rats PMRA #1897899	NOAEL = 11/14 mg/kg bw/day ♂/♀ LOAEL = 67/86 mg/kg bw/day ♂/♀, based on ↑ liver weight, ↑ liver eosinophilic cell foci, ↑ thyroid follicular cell hypertrophy, ↑ thyroid follicular epithelial desquamation, ↑ thyroid basophilic colloid; ↓ hind grip strength and ↑ hepatocyte hypertrophy (♂); ↓ bw, ↓ bwg, ALT, AST (♀) **Evidence of oncogenicity [thyroid follicular cell adenomas, hepatocellular adenomas (♂); uterine adenocarcinomas (♀)]. Dosing was considered adequate.**
1-generation reproduction (supplemental) Wistar rats PMRA #1897909	Effect levels were not established since this was a range-finding supplemental study. **Parental toxicity:** At 150 mg/kg bw/day, ↓ bw, ↓ bwg, ↓ fc, ↑ liver weights, ↑ abnormally darkened livers (♀) At 360 mg/kg bw/day, ↓ bw, ↓ bwg, ↓ fc (♂) **Reproductive toxicity:** At 360 mg/kg bw/day (exceeded MTD), ↓ implantation sites, ↓ # pups born **Offspring toxicity:** At 50 mg/kg bw/day, ↓ fc At 150 mg/kg bw/day, ↓ bw, ↑ liver weights At 360 mg/kg bw/day (exceeded MTD), ↓ bw, ↓ bwg, ↑ liver weight. ↑ # pup deaths LD 0-4, ↓ mean litter size, ↓ viability index, ↓ lactation index, ↑ missing pups (presumed cannibalized) Pups were kept with their mothers until LD 28 at which time, they were sacrificed.

Study Type/Animal/PMRA #	Study Results
2-generation reproduction (dietary) Wistar rats PMRA #1897908	**Parental toxicity:** NOAEL = 41/46 mg/kg bw/day ♂/♀, LOAEL = 120/143 mg/kg bw/day ♂/♀, based on ↓ bw, ↓ bwg, ↓ fc, ↑ liver weight, ↑ centrilobular heptocellular hypertrophy; enlarged liver (♀) **Reproductive toxicity:** NOAEL = 120 mg/kg bw/day ♂ LOAEL = not established ♂ In the absence of low (18 mg/kg bw/day) and mid (46 mg/kg bw/day) dose ovarian follicle data, a NOAEL was not determined in ♀ and a conservative POD of 18 mg/kg bw/day was considered to be a potential LOAEL. At 143 mg/kg bw/day, ↓ ovarian weight, ↓ primordial follicles (P), growing and antral follicles (F_1), ovarian corpora lutea (P), ↑ lactational diestrous **Offspring toxicity:** NOAEL = 46 mg/kg bw/day ♂/♀ LOAEL = 143 mg/kg bw/day ♂/♀, based on ↓ pup bw, delayed vaginal patency (F_1; equivocal), ↑ anogenital distance (♀; equivocal), ↑ liver weight (histopathology not conducted), ↓ spleen weight (histopathology not conducted) **Evidence of reproductive toxicity**
Developmental toxicity (gavage; supplemental) Wistar rats PMRA #1897911	Effect levels were not established since this was a range-finding supplemental study. **Maternal toxicity:** At 200 mg/kg bw/day, ↓ bwg when corrected for gravid uterine weight), ↓ fc At ≥500 mg/kg bw/day (exceeded MTD), ↑ clinical signs (↓ activity, ruffled fur, poor clinical condition, lateral recumbency, uncoordinated movements), ↓ bw, bw loss, ↓ fc Animals were sacrificed for humane reasons prior to study termination. At 750 mg/kg bw/day, 1 death (GD 11) **Developmental toxicity:** No treatment-related external or visceral malformations or variations.
Developmental toxicity (gavage) Wistar rats PMRA #1897910	Maternal NOAEL = 100 mg/kg bw/day Maternal LOAEL = 200 mg/kg bw/day, based on ↓ bw, ↓ bwg, ↓ fc Developmental NOAEL = 200 mg/kg bw/day Developmental LOAEL not established
Developmental toxicity (gavage; supplemental) NZW rabbits PMRA #1897913	Effect levels were not established since this was a range-finding supplemental study. **Maternal toxicity:** At ≥100 mg/kg bw/day, ↑ liver weight (histopathology was not conducted) At ≥300 mg/kg bw/day, ↓ defecation, ↓ bwg, ↓ fc At 500 mg/kg bw/day, ↑ mortality preceded by bw loss, ↓ fc, ↓ defecation and/or soft stool, ↓ bw **Developmental toxicity:** No treatment-related external or visceral malformations or variations.

Study Type/Animal/PMRA #	Study Results
Developmental toxicity (gavage) NZW rabbits PMRA #1897912	Maternal NOAEL = 100 mg/kg bw/day Maternal LOAEL = 200 mg/kg bw/day, based on slight ↑ abortions preceded by bw loss,↓/no fc, ↓ defecation, ↓ bwg/bw loss, ↓ fc Developmental NOAEL = 100 mg/kg bw/day Developmental LOAEL = 200 mg/kg bw/day, based on slight ↑ abortions, ↓ fetal weight **Evidence of developmental toxicity**
Gene mutations in bacteria PMRA #1897888	Negative
Gene mutations in mammalian cells in vitro PMRA #1897892	Negative
Chromosome aberrations in vitro PMRA #1897890	Negative
Unscheduled DNA synthesis (in vivo) PMRA #1897897	Negative
Micronucleus assay (in vivo) PMRA #1897894	Negative
28-day immunotoxicity (T-cell dependent antibody response of splenocyte assay) Supplemental CD-1 mice PMRA #1897837	Effect levels were not established since this was a supplemental study. High CV's were noted for the IgM data, which resulted in limited confidence in the study. At 1080 mg/kg bw/day, ↑ relative spleen weight, ↑ thymus weight; ↑ IgM AFC/10^6 Spleen cells, ↑ IgM AFC/Spleen ($\times 10^3$)

Study Type/Animal/PMRA #	Study Results
28-day comparative toxicity of the trans isomer, cis isomer and a racemic 1:1 mixture of sedaxane (dietary; supplemental) Wistar rats PMRA #1897840	Effect levels were not established since this was a supplemental study. The cis and trans isomers and sedaxane caused ↑ 16β hydroxylation of testosterone, consistent with being potent inducers of CYP 2B isoforms. The three test compounds caused ↓ 16α and 2α testosterone hydroxylation in males but increases in females. Both 16α and 2α are markers for the cytochrome isoenzyme CYP 2C11. The above findings were supported by ↑ CYP 2B and CYP 3A contents. The weakly ↑ EROD activity suggests that the cis and trans isomers and sedaxane do not act as polycyclic aromatic hydrocarbon-type inducers. Toxicokinetics: T_{max} =12-20 h; no obvious differences between the trans and cis isomers. C_{max} and AUC were ~10-fold lower in the cis isomer group vs. trans isomer group.
28-day toxicity (range-finding for the acute neurotoxicity study; supplemental) Wistar rats PMRA #1897917	Effect levels were not established since this was a range-finding supplemental study. At 80 mg/kg bw/day, ↑ piloerection (2-8 h post-dose), ↑ hunched posture, spasms, reduced activity also noted sporadically At ≥1000 mg/kg bw/day, ↑ reduced activity, hunched posture, spasms, piloerection, uncoordinated movements (peak effect at 3 h post-dose), ↓ bw, ↓ bwg
Acute neurotoxicity (gavage) Wistar rats PMRA #1897914	NOAEL = 30 mg/kg bw LOAEL = 250 mg/kg bw, based on reduced activity, decreased rearing, initial inactivity, piloerection; ruffled fur, recumbency, ↓ bw, ↓ bwg, ↓ fc (♂); weakened condition, swaying gait, decreased activity, reduced muscle tone, ↓ total distance (locomotor activity), ↓ rearing (♀)
28-day range-finding study for the 90-day neurotoxicity (dietary; supplemental) Wistar rats PMRA #1897919	Effect levels were not established since this was a range-finding supplemental study. At ≥154/156 mg/kg bw/day ♂/♀, ↓ fc; ↓ bw, ↓ bwg, ↓ fc (♀) At 360 mg/kg bw/day ♂, ↓ bw, ↓ bwg, ↓ fc (♂)
90-day neurotoxicity (dietary) Wistar rats PMRA #1897918	NOAEL = 66/80 mg/kg bw/day ♂/♀ LOAEL = 260/303 mg/kg bw/day ♂/♀, based on ↓ bw, ↓ bwg, ↓ fc, ↓ fe, ↓ locomotor activity

Study Type/Animal/PMRA #	Study Results
Metabolite Studies - CSCD465008	
Acute oral Wistar rats PMRA #1897921	Female LD_{50} > 2000 mg/kg bw Low Toxicity
28-day dietary Wistar rats PMRA #1897920	NOAEL = 1018/1107 mg/kg bw/day ♂/♀ LOAEL not established
Gene mutations in bacteria PMRA #1897924	Negative
Gene mutations in mammalian cells in vitro PMRA #1897922	Negative
Chromosome aberrations in vitro PMRA #1897923	Negative

Table 4 Toxicology Endpoints for Use in Health Risk Assessment for Sedaxane

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary general population	Acute neurotoxicity study (rats)	NOAEL = 30 mg/kg bw Clinical signs, decreased body weight, body weight gain and food consumption in males. Clinical signs, decreased activity, reduced muscle tone and decreased locomotor activity in females.	100
	ARfD = 0.3 mg/kg bw		
Repeated dietary	2-generation reproductive toxicity study (rats)	POD[2] = 18 mg/kg bw/day Decreased ovarian weight; decreased primordial follicles (P), growing and antral follicles (F_1), ovarian corpora lutea (P); increased lactational diestrous at 143 mg/kg bw/day Low and mid dose ovarian follicle counts were not assessed.	300
	ADI = 0.06 mg/kg bw/day		
Short-term to intermediate-term dermal[3] and inhalation[4]	2-generation reproductive toxicity study (rats)	POD[2] = 18 mg/kg bw/day Decreased ovarian weight; decreased primordial follicles (P), growing and antral follicles (F_1), ovarian corpora lutea (P); increased lactational diestrous at 143 mg/kg bw/day Low and mid dose ovarian follicle counts were not assessed.	300
Cancer	80-week oncogenicity study (mice) & 104/105-week chronic/oncogenicity study (rats)	Sedaxane exhibits oncogenic potential. There were treatment-related thyroid follicular cell tumours and hepatocellular tumours in male rats, uterine adenocarcinomas in female rats and hepatocellular tumours in male mice. An adjusted unit risk value (Q_1*) of 3.81×10^{-3} (mg/kg bw/day)$^{-1}$, for uterine adenocarcinomas was used for the cancer risk assessment and is protective of the other tumour types.	

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational assessments

[2] POD (point of departure)

[3] Since an oral NOAEL was selected, a dermal absorption factor (7%) was used in a route-to-route extrapolation

[4] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 5 Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN CANOLA			**PMRA # 1897931**
Radiolabel Position	[phenyl-U-^{14}C]-sedaxane and [pyrazole-5-^{14}C]-sedaxane		
Test Site	The treated canola seeds were sown into containers filled with sandy loam soil and maintained in a glasshouse with artificial lighting.		
Treatment	Seed treatment		
Rate	9.65-9.73 g a.i./100 kg seeds		
End-use product	Flowable concentrate (A14635)		
Pre-harvest Interval	Canola was harvested at maturity, 131-161 days after treatment and sowing on the same day.		
Matrix	**PHI (days)**	**[phenyl-U-^{14}C]-sedaxane**	**[pyrazole-5-^{14}C]-sedaxane**
		TRR (ppm)	**TRR (ppm)**
		Direct Determination	**Direct Determination**
Canola, seed	131-161	<0.002	<0.002
The total radioactive residues (TRRs) in canola were determined directly by combustion. Residues of sedaxane were not translocated into canola progeny seed following treatment.			
NATURE OF THE RESIDUE IN MAIZE			**PMRA # 1897930**
Radiolabel Position	[phenyl-U-^{14}C]-sedaxane and [pyrazole-5-^{14}C]-sedaxane		
Test Site	The treated maize seeds were sown into containers filled with sandy loam soil and maintained in a glasshouse with artificial lighting.		
Treatment	Seed treatment		
Rate	123.5-131.0 g a.i./100 kg seeds		
End-use product	Flowable concentrate (A14635)		
Pre-harvest Interval	Treated sweet corn and maize were harvested 75-76 days (sweet corn forage, kernels and cobs) , 83-85 days (maize forage) and 103-107 days (maize stover, kernels and cobs) after the seeds were treated and sown on the same day.		
Matrix	**PHI (days)**	**[phenyl-U-^{14}C]-sedaxane**	**[pyrazole-5-^{14}C]-sedaxane**
		TRR (ppm)	**TRR (ppm)**
		Direct Determination	**Direct Determination**
Sweet corn, forage	75	0.028	0.046
Sweet corn, cob (husks removed)	75-76	0.001	0.003
Sweet corn, kernel	75-76	<0.001	0.005
Maize, forage	83-85	0.027	0.057
Maize, stover	103-107	0.070	0.087
Maize, cob (husks removed)	103-107	0.006	0.006
Maize, grain	103-107	0.001	0.008
The TRRs, determined directly by combustion, in sweet corn and maize commodities were not further investigated.			
NATURE OF THE RESIDUE IN WHEAT			**PMRA # 1897930 and 1897933**
Radiolabel Position	[phenyl-U-^{14}C]-sedaxane and [pyrazole-5-^{14}C]-sedaxane		
Test Site	The treated spring wheat seeds were sown into containers filled with sandy loam soil and maintained in a glasshouse with artificial lighting.		
Treatment	Seed treatment		
Rate	41.5-42.5 g a.i./100 kg seeds		
End-use product	Flowable concentrate (A14635)		
Pre-harvest Interval	Treated spring wheat was harvested 27 days (forage), 48-55 days (hay) and 105-111 days (mature grain and straw) after the seeds were treated and sown on the same day.		

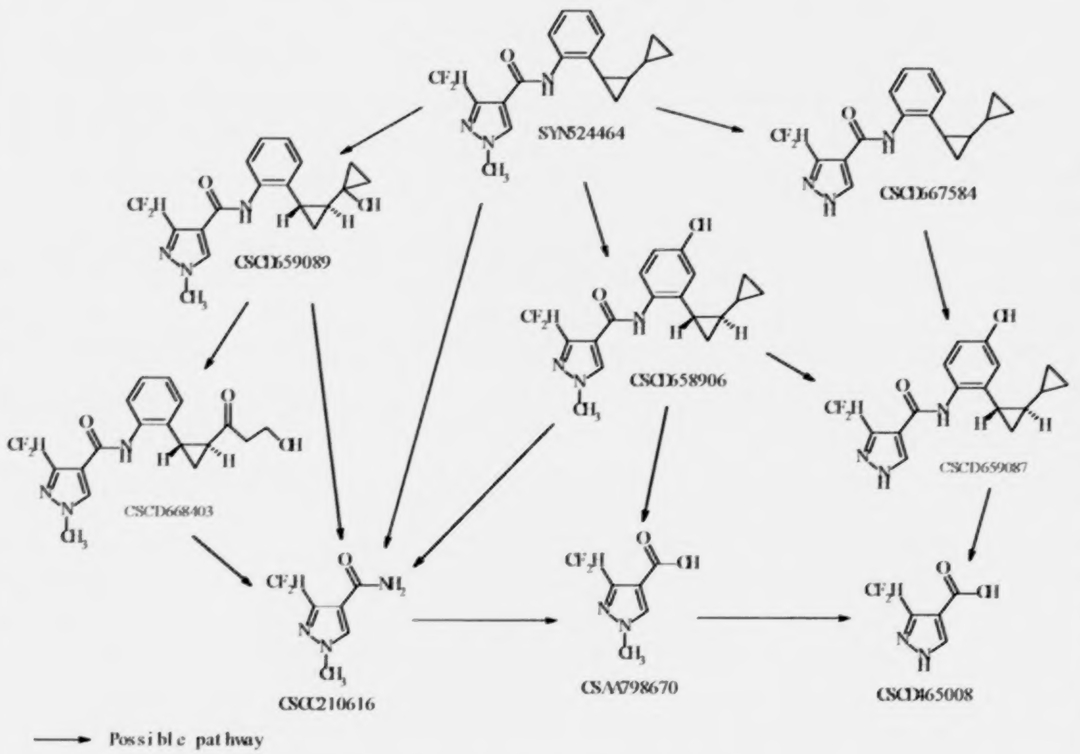
Matrix	**PHI (days)**	**[phenyl-U-^{14}C]-sedaxane**		**[pyrazole-5-^{14}C]-sedaxane**	
		TRR (ppm)		**TRR (ppm)**	
		Direct Determination	**Indirect Determination**	**Direct Determination**	**Indirect Determination**
Wheat, forage	27	0.435	0.451	0.610	0.606
Wheat, hay	48-55	0.762	0.730	1.042	1.041
Wheat, straw	105-111	1.005	1.132	0.805	0.884
Wheat, grain	105-111	0.005	Not applicable	0.007	Not applicable

The TRRs were determined directly by combustion and indirectly by summation of the radioactivity in the extracts and non-extractable solids. Due to the low levels of radioactivity in the grain (0.005-0.007 ppm), samples were not further investigated.

Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**[phenyl-U-^{14}C]-sedaxane**	**[pyrazole-5-^{14}C]-sedaxane**	**[phenyl-U-^{14}C]-sedaxane**	**[pyrazole-5-^{14}C]-sedaxane**
Wheat, forage	sedaxane; CSCD658906*; CSCD659089*; CSCD668403*;	sedaxane; CSCD658906*;	CSCD667584*; CSCD659087*	CSCD667584*; CSCD659089*; CSCD668403*; CSCD659087*; CSCC210616; CSCD465008
Wheat, hay	sedaxane;	sedaxane; CSCD658906*	CSCD667584*; CSCD658906*; CSCD659089*; CSCD668403*; CSCD659087*	CSCD667584*; CSCD659089*; CSCD668403*; CSCD659087*; CSCC210616
Wheat, straw	sedaxane; CSCD658906*	sedaxane; CSCD658906	CSCD667584*; CSCD659089*; CSCD668403*; CSCD659087*	CSCD667584*; CSCD659089*; CSCD668403*; CSCD659087*; CSCC210616; CSCD465008/ CSAA798670

*Total of the free and conjugated forms.

Proposed Metabolic Scheme of Sedaxane in Wheat



The principal metabolic transformations were hydroxylation of the phenyl ring, hydroxylation of the cyclopropyl ring and opening of the cyclopropyl ring. Minor metabolic transformations included N-demethylation of the pyrazole ring and cleavage between the pyrazole and phenyl rings. The trans:cis ratio of sedaxane in the analyzed wheat fractions was determined to be approximately 10:1. Only low levels of the pyrazole acids were detected, indicating that cleavage of the amide bond between the two aromatic rings is not a significant pathway in the metabolism of sedaxane.

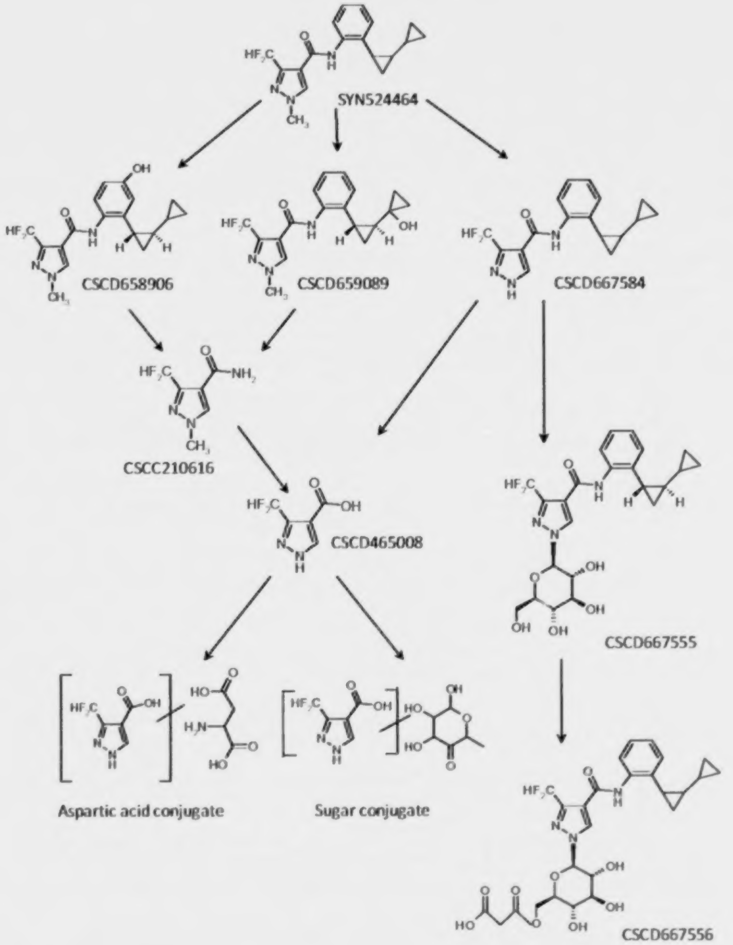
NATURE OF THE RESIDUE IN SOYBEAN	**PMRA # 1897930 and 1897932**
Radiolabel Position	[phenyl-U-^{14}C]-sedaxane and [pyrazole-5-^{14}C]-sedaxane
Test Site	The treated soybean seeds were sown into containers filled with sandy loam soil and maintained in a glasshouse with artificial lighting.
Treatment	Seed treatment
Rate	119.8-120.0 g a.i./100 kg seeds
End-use product	Flowable concentrate (A14635)
Pre-harvest Interval	Soybean was harvested 28 days (forage), 35-42 days (hay) and 96-103 days (progeny seed) after the seeds were treated and sown on the same day.

Matrix	PHI (days)	[phenyl-U-^{14}C]-sedaxane		[pyrazole-5-^{14}C]-sedaxane	
		TRR (ppm)		TRR (ppm)	
		Direct Determination	Indirect Determination	Direct Determination	Indirect Determination
Soybean, forage	28	0.132	0.138	0.123	0.123
Soybean, hay	35-42	0.419	0.354	0.427	0.438
Soybean, seed	96-103	0.009	0.009	0.054	0.055

The TRRs were determined directly by combustion and indirectly by summation of the radioactivity in the extracts and non-extractable solids. The TRRs in the extracts of soybean seed (phenyl label) were not further investigated.

Metabolites Identified	Major Metabolites (> 10% TRR)		Minor Metabolites (< 10% TRR)	
Radiolabel Position	[phenyl-U-^{14}C]-sedaxane	[pyrazole-5-^{14}C]-sedaxane	[phenyl-U-^{14}C]-sedaxane	[pyrazole-5-^{14}C]-sedaxane
Soybean, forage	sedaxane; CSCD667555; CSCD667556	sedaxane; CSCD667555; CSCD667556	CSCD667584; CSCD658906; CSCD659089	CSCD667584; CSCD658906; CSCD659089; CSCD465008; CSCC210616
Soybean, hay	sedaxane; CSCD667555; CSCD667556	sedaxane; CSCD667555; CSCD667556	CSCD667584; CSCD658906; CSCD659089	CSCD667584; CSCD658906; CSCD465008; CSCC210616
Soybean, seed	Not analyzed	CSCD465008 (sugar conjugate)	Not analzyed	CSCD465008; CSCD465008 (aspartic acid conjugate)

Proposed Metabolic Scheme of Sedaxane in Soybean


SYN524464
CSCD658906
CSCD659089
CSCD667584
CSCC210616
CSCD465008
CSCD667555
Aspartic acid conjugate
Sugar conjugate
CSCD667556

CSCD658906 and CSCD659089 were detected at very low levels in initial analyses

The principal transformation included N-demethylation of the pyrazole ring of sedaxane and subsequent conjugation with glucose followed by malonic acid; cleavage between the pyrazole and phenyl rings; and asparatic acid and sugar conjugation of the pyrazole acid CSCD465008. Sedaxane was not detected in soybean seed. No major phenyl-specific metabolites were identified in any of the soybean commodities analyzed. The trans:cis isomer ratio of sedaxane in soybean forage (pyrazole label) and soybean hay (phenyl label) was approximately 4:3 and 3:1, respectively.

NATURE OF THE RESIDUE IN SWISS CHARD	**PMRA # 1897934**
Radiolabel Position	[phenyl-U-^{14}C]-sedaxane and [pyrazole-5-^{14}C]-sedaxane
Test Site	The treated Swiss chard seeds were sown into containers filled with sandy loam soil and maintained in a glasshouse with artificial lighting.
Treatment	Seed treatment
Rate	41.6-42.4 g a.i./100 kg seeds

End-use product	Flowable concentrate (A14635)
Pre-harvest Interval	Swiss chard was harvested 49 days after the seeds were treated and sown on the same day.

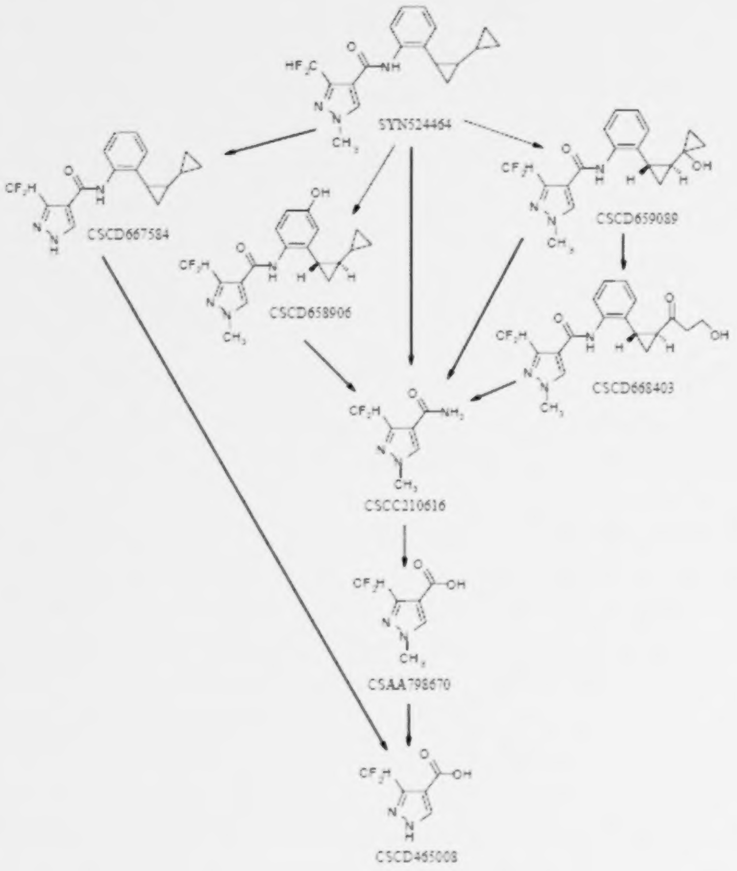
Matrix	**PHI (days)**	**[phenyl-U-^{14}C]-sedaxane**		**[pyrazole-5-^{14}C]-sedaxane**	
		TRR (ppm)		**TRR (ppm)**	
Swiss chard	49	**Direct Determination**	**Indirect Determination**	**Direct Determination**	**Indirect Determination**
		0.0491	0.0452	0.0586	0.0556

The TRRs were determined directly by combustion and indirectly by summation of the radioactivity in the extracts and non-extractable solids.

Metabolites Identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**[phenyl-U-^{14}C]-sedaxane**	**[pyrazole-5-^{14}C]-sedaxane**	**[phenyl-U-^{14}C]-sedaxane**	**[pyrazole-5-^{14}C]-sedaxane**
Swiss chard	sedaxane	sedaxane*; CSCD465008*; CSCC210616*	CSCD667584; CSCD658906/ CSCD659089[1]*; CSCD668403*	CSCD667584; CSCD658906/ CSCD659089[1]*; CSCD668403*; CSAA798670*

*Total of the free and conjugated forms. [1]Tentative assignment.

Proposed Metabolic Scheme of Sedaxane in Swiss Chard



Based on tentative assignments of CSCD659089, CSCD658906 and CSCD668403 →

No phenyl specific metabolites were identified in Swiss chard. The trans:cis ratio of sedaxane was determined to be approximately 10:1. The principal metabolic transformations of sedaxane in Swiss chard include N-demethylation of the pyrazole ring and cleavage between the pyrazole and phenyl rings. Possible minor transformations were hydroxylation of the phenyl ring and/or hydroxylation of the cyclopropyl ring, and opening of the cyclopropyl ring.

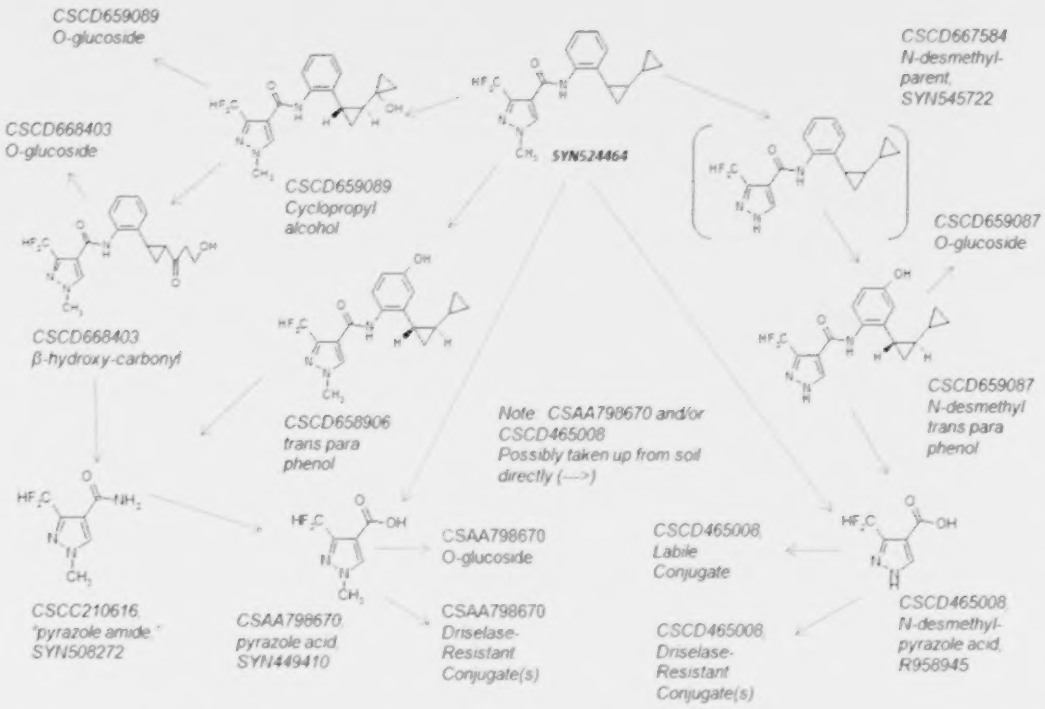
CONFINED ACCUMULATION IN ROTATIONAL CROPS – Lettuce, radish and wheat		**PMRA # 1897976**
Radiolabel Position	**[phenyl-U-^{14}C]-sedaxane**	**[pyrazole-5-^{14}C]-sedaxane**
Test site	Twelve outdoor plots (four for each the phenyl label, pyrazole label and controls, respectively) were established in Madera, California. Each plot consisted of above-ground wooden boxes filled with sandy loam soil.	

Formulation used for trial	A14950A
Application rate and timing	Soybean seeds pre-coated with phenyl- and pyrazole- radiolabeled sedaxane were planted in bare soil and were allowed to germinate. The seeding rate was 90-93 seeds/plot in order to achieve the target application rate of 100 g a.i./ha. The actual application rates were 99-113 g a.i./ha. The soybean plants were cut and re-tilled back into the soil within 0-7 days prior to plant of the secondary crops. After tilling the soybean plants back into the soil, seeds were planted as follows: lettuce (30-, 151- and 365- day PBI), radish (30-, 120- and 365-day PBI) and wheat (30-, 120- and 365-day PBI). The 365-day PBI seeds were re-planted into the original 30-day PBI plots requiring no re-tilling of soybean plants. PBI = plantback interval

Metabolites Identified		**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Matrix	**PBI (days)**	**[phenyl-U-^{14}C]-sedaxane**	**[pyrazole-5-^{14}C]-sedaxane**	**[phenyl-U-^{14}C]-sedaxane**	**[pyrazole-5-^{14}C]-sedaxane**
Lettuce, Immature	30	sedaxane; CSCD668403	CSAA798670*; CSCD465008*	None	sedaxane; CSCD668403
	151	sedaxane; CSCD659087	CSAA798670*; CSCD465008*	CSCD658906	sedaxane
	365	sedaxane	CSAA798670*; CSCD465008*	CSCD659087; CSCD659089	None
Lettuce, Mature	30	CSCD659089	sedaxane; CSAA798670*; CSCD465008*	None	None
	151	None	CSAA798670*; CSCD465008*	sedaxane; CSCD659089	sedaxane; CSCC210616
	365	sedaxane	CSAA798670*; CSCD465008*	CSCD659087	-
Radish Foliage	30	sedaxane; CSCD668403; CSCD659089	sedaxane; CSCD668403; CSCD465008; CSCC210616	None	CSCD659089
	120	CSCD668403; CSCD659087; CSCD659089	CSCD465008* ; CSCC210616	sedaxane	sedaxane; CSCD668403*; CSCD659087*; CSCD659089; CSCD658906*; CSAA798670*;
	365	CSCD668403	CSCD465008*	None	CSCC210616
Radish Root	30	sedaxane	sedaxane	None	None
	120	sedaxane	sedaxane; CSCD465008*; CSCC210616	None	None
	365	Not analyzed	CSCD465008*; CSCC210616	Not analyzed	sedaxane
Wheat Forage	30	CSCD668403*; CSCD659089*	CSCD668403*; CSCD659089*; CSAA798370*; CSCD465008*	sedaxane; CSCD659087*	sedaxane; CSCD659087*
	120	sedaxane; CSCD668403*; CSCD659089*	CSCD668403*; CSCD659089*; CSAA798670*; CSCD465008*	CSCD659087*	sedaxane; CSCD659087*

	365	CSCD668403*; CSCD659087*; CSCD659089*	CSCD668403*; CSCD659089*; CSAA798670*; CSCD465008*	sedaxane	sedaxane; CSCD659087*
Wheat, Hay	30	CSCD668403*; CSCD659089*	CSCD668403*; CSCD659089*; CSAA798670*; CSCD465008*	sedaxane; CSCD659087*	sedaxane; CSCD659087*
	120	CSCD659087*; CSCD659089*	CSCD668403*; CSCD659089; CSAA798670; CSCD465008	None	CSCD659087*
	365	CSCD668403*;	CSCD668403*; CSAA798670*; CSCD465008*	sedaxane; CSCD659087*; CSCD659089*; CSCD658906	CSCD659087*; CSCD659089*; CSCD658906; CSCC210616
Wheat ,Straw	30	CSCD668403*; CSCD659089*	CSCD659089*; CSAA798670*; CSCD465008*	sedaxane; CSCD659087*	sedaxane; CSCD668403*; CSCD659087*;
	120	CSCD668403*; CSCD659089*	CSCD668403*; CSCD659089*; CSAA798670*; CSCD465008*	sedaxane; CSCD659087*	sedaxane; CSCD659087*
	365	CSCD668403*; CSCD659087*; CSCD659089*	CSCD659089*; CSAA798670*	sedaxane	sedaxane; CSCD668403*; CSCD659087*; CSCD465008*
Wheat, grain	30	Not analyzed			
	120	Not analyzed	CSCD465008*	Not analyzed	None
	365	Not analyzed			
*Total of the free and conjugated forms.					

Proposed Metabolic Scheme of Sedaxane in Rotational Crops
Seed Treatment Application


CSCD659089
O-glucoside
CSCD668403
O-glucoside
CSCD659089
Cyclopropyl
alcohol
SYN524464
CSCD667584
N-desmethyl-
parent,
SYN545722
CSCD659087
O-glucoside
CSCD668403
β-hydroxy-carbonyl
CSCD658906
trans para
phenol
Note: CSAA798670 and/or
CSCD465008
Possibly taken up from soil
directly (—>)
CSCD659087
N-desmethyl
trans para
phenol
CSAA798670
O-glucoside
CSCD465008,
Labile
Conjugate
CSCC210616,
"pyrazole amide,"
SYN508272
CSAA798670,
pyrazole acid,
SYN449410
CSAA798670
Driselase-
Resistant
Conjugate(s)
CSCD465008
Driselase-
Resistant
Conjugate(s)
CSCD465008,
N-desmethyl-
pyrazole acid,
R958945

Sedaxane and/or *N*-desmethylated sedaxane is hydroxylated on the phenyl or bicyclo rings, and/or is cleaved at the amide bridge. Once cleaved, the phenyl moiety does not appear as a significant residue in plants. The remaining pyrazole moiety, as either a pyrazole amide, pyrazole acid and/or *N*-desmethyl pyrazole acid, degrades further at a comparatively slow rate. The hydroxylated intact metabolites (CSCD668403, CSCD659087 and CSCD659089), as well as the pyrazole acid (CCAA798670) and *N*-desmethyl pyrazole acid (CSCD465008), were present in both free and conjugated forms.

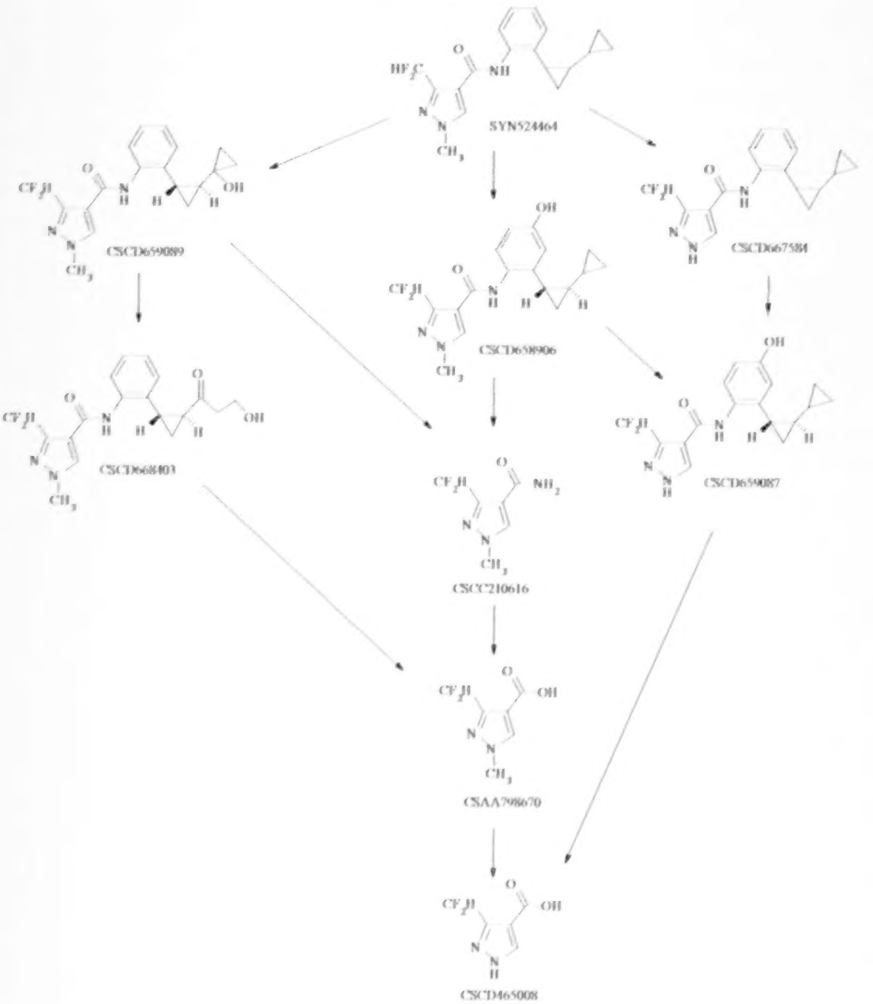
CONFINED ACCUMULATION IN ROTATIONAL CROPS – Lettuce, turnip and Spring Wheat		**PMRA # 1897974**
Radiolabel Position	**[phenyl-U-^{14}C]-sedaxane**	**[pyrazole-5-^{14}C]-sedaxane**
Test site	The biological phase was conducted under glasshouse conditions in the United Kingdom. Plastic containers were filled with sandy loam soil. Prior to the addition of the soil, a layer (~5 cm) of polystyrene beads was added to the bottom of each container to aid drainage.	
Formulation used for trial	Flowable concentrate (A14635)	
Application rate and timing	The soil in each container was sprayed with radiolabeled sedaxane using a hand-powered sprayer. The target application rate was 100 g a.i./ha. The actual application rates were 102.6-107.7 g a.i./ha No tilling took place after application of the test substance. Crops were sown at 29, 90 and 300 days after application. PBI = plant-back interval.	

Metabolites Identified		**Major Metabolites (>10% TRR)**		**Minor Metabolites (<10% TRR)**	
Matrix	**PBI (days)**	**[phenyl-U-^{14}C]-sedaxane**	**[pyrazole-5-^{14}C]-sedaxane**	**[phenyl-U-^{14}C]-sedaxane**	**[pyrazole-5-^{14}C]-sedaxane**
Lettuce, Immature	29	sedaxane	sedaxane; CSCD465008/ CSAA798670	CSCD667584	CSCD667584; CSCD659089
	90	Sedaxane; CSCD667584	sedaxane; CSCD465008/ CSAA798670	CSCD659089; CSCD668403	CSCD667584; CSCD659089
	300	Not analyzed	CSCD465008/ CSAA798670	Not analyzed	sedaxane; CSCD667584
Lettuce, Mature	29	sedaxane	sedaxane; CSCD465008/ CSAA798670	CSCD667584	CSCD667584; CSCD659089; CSCD6687403
	90	sedaxane	sedaxane; CSCD465008/ CSAA798670	CSCD667584; CSCD659089; CSCD668403	CSCD667584; CSCD659089
	300	Not analyzed	CSCD465008/ CSAA798670	Not analyzed	sedaxane; CSCD667584
Turnip, Leaves	29	sedaxane	CSCD465008*; CSCC210616*	CSCD667584; CSCD658906*; CSCD659089*; CSCD668403*; CSCD659087*	sedaxane; CSCD667584*; CSCD6598906*; CSCD659089*; CSCD659087*; CSAA798670*
	90	sedaxane	CSCD465008*; CSAA798670*	CSCD667584; CSCD659089*	sedaxane; CSCD667584; CSCD659089*; CSCC210616*
	300	None	CSCD465008/ CSAA798670	sedaxane; CSCD667584; CSCS659089	sedaxane; CSCD667584; CSCD659089; CSCC210616
Turnip, Roots	29	sedaxane	sedaxane; CSCD465008/ CSAA798670	CSCD667584; CSCD658906; CSCD659089	CSCD667584; CSCD658906
	90	sedaxane; CSCD667584	sedaxane; CSCD465008/ CSAA798670	CSCD658906	CSCD667584
	300	Not analyzed			

Wheat, Forage	29	sedaxane; CSCD659089*	sedaxane; CSCD659089*; CSAA798670*	CSCD667584; CSCD658906*; CSCD668403*	CSCD667584; CSCD658906*; CSCD668403*; CSCD659087; CSCD465008*; CSCC210616*
	90	sedaxane; CSCD659089*;	sedaxane; CSCD465008*; CSAA798670*; CSCD465008*	CSCD667584; CSCD658906*; CSCD668403*; CSCD659087*	CSCD667584; CSCD658906*; CSCD659089*; CSCD668403*; CSCD659087*; CSCC210616*
	300	sedaxane	sedaxane; CSCD465008*	CSCD667584; CSCD658906*; CSCD659089*; CSCD668403*; CSCD659087*	CSCD667584; CSCD658906*; CSCD659089*; CSCD668403*; CSCD659087*; CSAA798670*; CSCC210616*
Wheat, Hay	29	sedaxane	sedaxane	CSCD667584; CSCD658906*; CSCD659089*; CSCD668403*; CSCD659087*	CSCD667584; CSCD658906*; CSCD659089*; CSCD668403*; CSCD659087*; CSCD465008*; CSAA798670*; CSCC210616*
	90	sedaxane	sedaxane; CSCD465008*; CSAA798670*	CSCD667584; CSCD658906*; CSCD659089*; CSCD668403*; CSCD659087*	CSCD667584; CSCD658906*; CSCD659089*; CSCD668403*; CSCD659087*; CSCC210616*
	300	sedaxane	sedaxane	CSCD667584; CSCD658906*; CSCD659089*; CSCD668403*; CSCD659087*	CSCD667584; CSCD658906*; CSCD659089*; CSCD668403*; CSCD659087*; CSCD465008*; CSAA798670*; CSCC210616*

Wheat, straw	29	sedaxane; CSCD659089*	sedaxane	CSCD667584; CSCD658906*; CSCD668403*; CSCD659087*	CSCD667584; CSCD658906*; CSCD659089*; CSCD668403*; CSCD659087*; CSCD465008*; CSAA798670*; CSCC210616*
	90	sedaxane	sedaxane; CSCD465008*; CSAA798670*	CSCD667584; CSCD658906*; CSCD659089*; CSCD668403*; CSCD659087*	CSCD667584; CSCD658906*; CSCD659089*; CSCD668403*; CSCD659087*; CSCC210616*
	300	sedaxane; CSCD659089*	sedaxane	CSCD667584; CSCD658906*; CSCD668403*; CSCD659087*	CSCD667584; CSCD658906*; CSCD659089*; CSCD668403*; CSCD659087*; CSCD465008*; CSAA798670*; CSCC210616*
Wheat, grain	29	sedaxane; CSCD667584	None	CSCD659089	sedaxane; CSCD667584; CSCD659089; CSCD465008/ CSAA798670
	90	None	None	sedaxane; CSCD667584; CSCD659089	sedaxane; CSCD667584; CSCD659089
	300	Not analyzed			

Proposed Metabolic Scheme of Sedaxane in Rotational Crops
Bare Soil Application


SYN524464
CSCD659089
CSCD658906
CSCD667584
CSCD668403
CSCC210616
CSCD659087
CSAA798670
CSCD465008

The proposed biotransformation pathway for sedaxane involves N-demethylation of the pyrazole ring; hydroxylation of the phenyl ring; hydroxylation of the cyclopropyl ring; conjugation of primary metabolites; opening of the cyclopropyl ring; and cleavage of the amide bond between the two aromatic rings.

NATURE OF THE RESIDUE IN LAYING HEN	PMRA #1897936

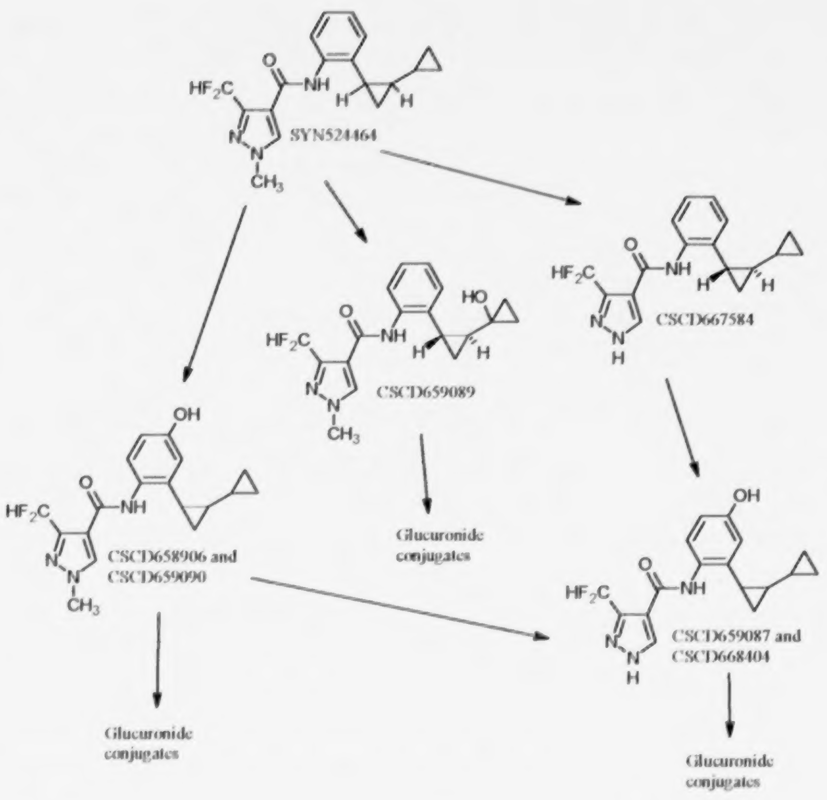
Five laying hens each were dosed orally by gelatin capsule with either [pyrazole-5-^{14}C]-sedaxane or with [phenyl-U-^{14}C]-sedaxane. One hen dosed with the phenyl labeled sedaxane was sacrificed early due to poor health and was not included in the study. The nominal dose rate was 12 mg/kg/day (calculated based on feed dry matter) and dosing continued for 14 consecutive days. The actual mean doses were 18.7-21.6 ppm (phenyl label) and 18.1-23.5 ppm (pyrazole label). Eggs were collected twice daily throughout the study (yolk and white were separated); excreta and cage wash were collected once daily. The birds were sacrificed approximately 12 hours after the final dose. Samples of liver, peritoneal fat, subcutaneous fat with skin attached, and muscle (combined leg and thigh, and breast) were collected for analysis.

Matrices	**% of Administered Dose (Mean)**	
	[phenyl-U-^{14}C]-sedaxane	**[pyrazole-5-^{14}C]-sedaxane**
Excreta	89.03	93.75
Cage Wash	5.30	4.35
Egg White (Day 9-14 Composite)	<0.01	0.01
Egg Yolk (Day 9-14 Composite)	0.03	0.03
Partially Formed Eggs	0.02	0.02
Abdominal Fat	<0.01	<0.01
Liver	0.04	0.03
Muscle (Leg and Thigh)	Not reported	Not reported
Muscle (Muscle Breast)	Not reported	Not reported

Metabolites identified	**Major Metabolites (>10% TRR)**		**Minor Metabolites (<10% TRR)**	
Radiolabel Position	**[phenyl-U-^{14}C]-sedaxane**	**[pyrazole-5-^{14}C]-sedaxane**	**[phenyl-U-^{14}C]-sedaxane**	**[pyrazole-5-^{14}C]-sedaxane**
Egg Yolk	CSCD658906*	CSCD658906*	edaxane; CSCD667584; CSCD659090*	sedaxane; CSCD667584; CSCD659090*; CSCD668404/ CSCD659087*; CSCD659089*
Egg White	sedaxane; CSCD667584	-	-	sedaxane; CSCD667584
Muscle	sedaxane	-	CSCD667584	sedaxane; CSCD667584
Liver	CSCD658906*	CSCD658906*	CSCD659090*; CSCD668404/ CSCD659087*	CSCD659090*; CSCD668404/ CSCD659087*
Abdominal Fat	sedaxane	sedaxane	CSCD667584	CSCD667584
Skin and Fat	sedaxane	sedaxane	CSCD667584	CSCD667584

*Total of the free and conjugated forms.

Proposed Metabolic Scheme in the Laying Hen



The primary mechanisms for the proposed biotransformation pathway of sedaxane in the laying hen were: N-demethylation; hydroxylation of the phenyl ring of sedaxane to give the para phenols CSCD658906 and CSCD659090 and the cyclopropyl alcohol CSCD659089; and O-glucuronidation of the hydroxylated metabolites of sedaxane and N-desmethyl sedaxane.

NATURE OF THE RESIDUE IN LACTATING GOAT	PMRA #1897937 and 1897981

Two lactating goats each were dosed orally by gelatin capsule with either [pyrazole-5-^{14}C]-sedaxane or with [phenyl-U-^{14}C]-sedaxane at mean dosing levels of 24.0 ppm (phenyl label) and 22.8 ppm (pyrazole label) in the diet for 7 consecutive days. Milk was collected twice daily throughout the study, in the morning before dose administration and in the afternoon; urine and feces were collected daily. Tissues, including muscle (composite of forequarter, hindquarter, and tenderloin), fat (composite of perirenal, omental, and subcutaneous), liver, and kidneys, were collected at sacrifice, approximately 12 hours after the final dose.

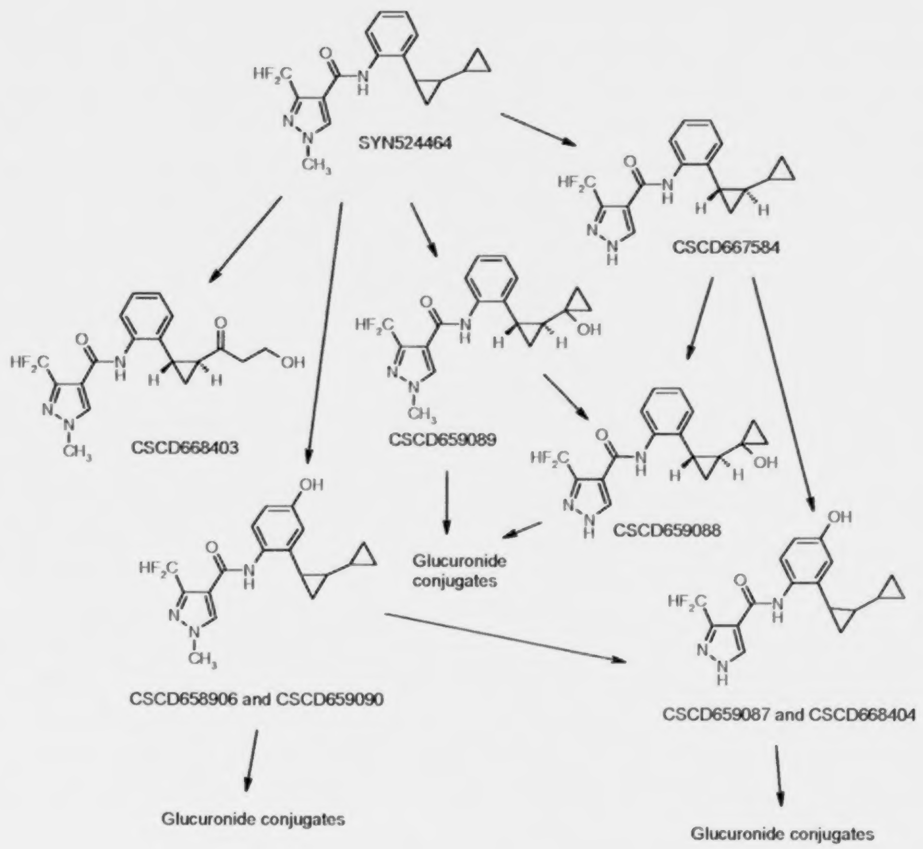
A separate study was conducted to investigate the behavior of sedaxane derived N-glucose conjugates found in soybean following incubation with rumen fluid. Extracts of soya hay were incubated with a buffered mineral solution (RPT medium) containing rumen fluid (9:1, v/v) at 39°C and under a CO_2 atmosphere. The reactions were terminated after 0, 4, 24, 48 and 96h of incubation, respectively. A control experiment, contained only soya hay extract and the buffered mineral solution (RPT medium), was run concurrently with the rumen fluid experiment in order to assess the effect of RPT medium on the soya metabolites in the absence of the rumen fluid. The results indicate that rumen microflora have the capability to cleave the *N*-linked glucose and malonyl glucose conjugates of desmethyl sedaxane (CSCD667584) rapidly and quantitatively.

Matrices	**% of Administered Dose**	
	[phenyl-U-^{14}C]-sedaxane	**[pyrazole-5-^{14}C]-sedaxane**
Urine	26.10	18.39
Feces	49.44	62.05
Total Excreted	75.54	80.44
Milk (Total Days 1-7)	0.11	0.13
Muscle	Not applicable*	Not applicable*
Fat	Not applicable*	Not applicable*
Kidney	0.01	<0.01
Liver	0.22	0.16
GI Tract Contents	9.28	6.20
Bile	0.08	0.17

*Whole tissue not collected.

Metabolites identified	**Major Metabolites (> 10% TRR)**		**Minor Metabolites (< 10% TRR)**	
Radiolabel Position	**[phenyl-U-^{14}C]-sedaxane**	**[pyrazole-5-^{14}C]-sedaxane**	**[phenyl-U-^{14}C]-sedaxane**	**[pyrazole-5-^{14}C]-sedaxane**
Fat	sedaxane; CSCD667584	sedaxane; CSCD667584	-	-
Kidney	CSCD658906*; CSCD659088*; CSCD668404/ CSCD659087*	CSCD658906*; CSCD668404/ CSCD659087*	CSCD659090*; CSCD659089*	CSCD659090*; CSCD659088*; CSCD659089*
Liver	CSCD658906*	CDCD658906*	sedaxane; CSCD667584; CSCD659090*; CSCD659088*; CSCD668404/ CSCD659087*; CSCD659089*	sedaxane; CSCD667584; CSCD659090*; CSCD668404/ CSCD659087*; CSCD659089*
Milk	-	-	CSCD658906*; CSCD659088*; CSCD668404/ CSCD659087*	CSCD667584; CSCD658906*; CSCD659088*; CSCD668404/ CSCD659087*

Proposed Metabolic Scheme in the Lactating Goat


SYN524464
CSCD667584
CSCD668403
CSCD659089
CSCD659088
Glucuronide conjugates
CSCD658906 and CSCD659090
CSCD659087 and CSCD668404
Glucuronide conjugates
Glucuronide conjugates

The primary mechanisms for the proposed biotransformation pathway of sedaxane in lactating goat were: N-demethylation; hydroxylation of sedaxane to give the para phenols CSCD658906 and CSCD659090 and the cyclopropyl alcohol CSCD659089; hydroxylation of desmethyl sedaxane to give the para phenols CSCD659087 and CSCD668404 and the desmethyl cyclopropyl alcohol CSCD659088; opening of the terminal cyclopropyl moiety of sedaxane followed by oxidation of side chain to give a β-hydroxycarbonyl sedaxane metabolite (the trans isomer CSCD668403 was identified); and conjugation of hydroxylated metabolites and desmethyl sedaxane.

STORAGE STABILITY- CROP AND PROCESSED COMMODITIES	PMRA # 1897927; 1897925; 1897928; 1897929
The storage stability data indicate that residues of the two sedaxane isomers (SYN508210 and SYN508211) are stable at ≤-18 °C for 24 months in wheat grain, wheat straw, spinach, potato, orange, lentils, and soybeans. The interim results of the 24-month study indicate that residues of the metabolites CSCD667584, CSCD658906, CSCD659089, CSCD668403, CSCD667555 and CSCC210616 are stable at ≤-18 °C for 6 months in wheat grain, wheat straw, spinach leaves, potato tuber, orange (fruit), dried broad beans, and soybean seeds; and residues of CSCD465008 are stable at a ≤ -18 °C for 6 months in orange (fruit), dried broad beans, and soybean seeds. The storage stability data indicate that residues of CSCD465008 and CSAA798670 are stable at ≤-18 °C for 12 months in wheat grain, wheat straw, barley forage, spinach leaves, carrot leaves, and carrot roots. The interim results of the 12-month study indicate that residues of SYN508210 and SYN508211 are stable at approximately -20 °C for 6 months in processed commodities of wheat (flour, germ, and bran), soybean (meal, hulls, and oil) and orange (dried pulp, juice, and oil) (PMRA No. 1897929). The interim 4-month results of the 12-month study for the metabolite CSCD465008 in soybean processed commodities (hulls, meal and oil) are inconclusive. The results for the 6- and 12-month storage intervals are needed to confirm the stability of this metabolite in soybean processed commodities.	
STORAGE STABILITY- LIVESTOCK COMMODITIES	**PMRA # 1897971**
A storage stability study was not submitted and is not required for the purposes of these submissions. It is stated in DIR98-02 (Section 5- Storage Stability Data) that storage stability data will not be needed for samples stored frozen for less than 30 days. During the dairy cattle feeding study, the maximum interval of frozen storage prior to extraction were 20 days for milk samples, including skimmed milk and cream, and 17 days for tissue samples.	

CROP FIELD TRIALS ON BARLEY	**PMRA # 1897954, 1897952 and 1898338**

A sufficient number of trials were conducted in NAFTA representative Regions in order to evaluate the magnitude of sedaxane residues in/on barley.

US Trials

A flowable concentrate formulation of sedaxane (SYN524464 FS) was applied as a seed treatment to barley at a target rate of 5 g a.i./100 kg seed. Prior to application of the test material, the seed received a maintenance treatment of fungicide and/or insecticide. Single control and duplicate treated samples of barley hay were harvested from each plot 45 days after planting (DAP), and barley straw and grain were harvested at maturity. At one trial site, a decline study was undertaken for barley hay, straw and grain.

Canadian Trials

Barley seed were treated with a flowable concentrate formulation of sedaxane (A16148C) at a target rate of 5 g a.i./100 kg seed. Single control and duplicate treated samples of barley hay were collected at growth stages BBCH 73-85, except for one untreated sample at BBCH 59, from 60-77 days after planting. Samples of barley grain and straw were collected at commercial harvest (BBCH 87-99), from 95-119 DAP. At one trial site, a decline study was undertaken for barley hay, straw and grain.

Side-by-side field trials were also conducted in Canada for sedaxane in/on barley target rate of 5-5.2 g a.i./100 kg seed) when used as a seed treatment combination product with two other currently registered active ingredients (sedaxane/ difenoconazole/metalaxyl-M FS formulation) or three other currently registered active ingredients (sedaxane/difenoconazole/metalaxyl-M/thiamethoxam FS formulation). Residues of sedaxane were determined in barley hay and grain.

For all trials, barley samples were analyzed for residues of sedaxane (as the 2 isomers SYN50810 and SYN508211), and the metabolites CSCD667584, CSCD658906, CSCD667555 (including contribution from the N-malonyl conjugate CSCD667556) and CSCD465008 using Method GRM023.03A (LC-MS/MS). The LOQ was 0.005 ppm for each sedaxane isomer and 0.01 ppm for each metabolite. Given the residue definition is sedaxane, both for enforcement and risk assessment, only the combined residues of the two sedaxane isomers, SYN508210 and SYN508211, are reported.

For the residue decline trial conducted in the US, total sedaxane residues (SYN508210 and SYN508211) did not accumulate in barley hay; and were not detected above the LOQ in/on straw and grain at any sampling interval.

For the residue decline trial conducted in Canada, residues of sedaxane (SYN508210 and SYN508211) were not detected above the LOQ in/on barley hay, grain or straw at any sampling interval.

Commodity	**Total application (g a.i./100 kg seed)**	**n**	**Min.**	**Max.**	**HAFT**	**Median (STMdR)**	**Mean (STMR)**	**Std. Dev.**
Total Sedaxane Residues (SYN508210 + SYN508211)								
US Trials								
Barley, Forage	5	24	<0.01	<0.025	<0.025	0.010	0.013	0.006
Barley, Straw		24	<0.01	<0.01	<0.01	<0.01	<0.01	0
Barley, Grain		24	<0.01	<0.01	<0.01	<0.01	<0.01	0
Canadian Trials								
Barley, Hay	5-5.2	36	<0.01	<0.01	<0.01	<0.01	<0.01	0
Barley, Straw		24	<0.01	<0.01	<0.01	<0.01	<0.01	0
Barley, Grain		36	<0.01	<0.01	<0.01	<0.01	<0.01	0

CROP FIELD TRIALS ON CANOLA

PMRA # 1897960 and 1897968

A sufficient number of trials were conducted in NAFTA representative Regions in order to evaluate the magnitude of sedaxane residues in/on canola.

US Trials

A flowable concentrate formulation of sedaxane (SYN524464 FS) was applied as a seed treatment to canola at a target rate of 7.5 g a.i./100 kg seed. Prior to application of the test material, the canola seed also received a maintenance treatment of insecticide. Single control and duplicate treated canola seed samples were collected at maturity (84 to 232 DAP). A residue decline study was conducted at one trial site.

Canadian Trials

Canola seeds were treated with a flowable concentrate formulation (A16148C) of sedaxane, at a target rate of 5.9 g a.i./100 kg seed. Single control and duplicate treated samples of canola seed were collected at normal commercial harvest (BBCH 89), 91-132 DAP. A residue decline study was conducted at two trial sites.

For all trials, canola samples were analyzed for residues of sedaxane (as the 2 isomers SYN50810 and SYN508211), and the metabolites CSCD667584, CSCD658906, CSCD667555 (including contribution from the N-malonyl conjugate CSCD667556) and CSCD465008 using Method GRM023.03A (LC-MS/MS). The LOQ was 0.005 ppm for each sedaxane isomer and 0.01 ppm for each metabolite. Given the residue definition is sedaxane, both for enforcement and risk assessment, only the combined residues of the two sedaxane isomers, SYN508210 and SYN508211, are reported.

In the residue decline trials conducted in the US and Canada, residues of the two sedaxane isomers were each less than the LOQ in/on seed at all sampling intervals.

Commodity	Total application (g a.i./100 kg seed)	n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Total Sedaxane Residues (SYN508210 + SYN508211)								
US Trials								
Canola, Seed	7.5	16	<0.01	<0.01	<0.01	<0.01	<0.01	0
Canadian Trials								
Canola, Seed	5.9	32	<0.01	<0.01	<0.01	<0.01	<0.01	0

CROP FIELD TRIALS ON SOYBEAN

PMRA # 1897964

A sufficient number of trials were conducted in NAFTA representative Regions in order to evaluate the magnitude of sedaxane residues in/on soybean.

US Trials

A flowable concentrate formulation of sedaxane (SYN524464 FS) was applied as a seed treatment to soybean at a target rate of 40 g a.i./100 kg seed. Prior to application of the test material, the soybean seed also received a maintenance treatment of fungicide. Single control and duplicate treated samples of soybean forage and hay were harvested from each plot 45 DAP, and soybean seed was harvested at maturity. A residue decline study was conducted at two trial sites for soybean forage, hay and seed.

Soybean samples were analyzed for residues of sedaxane (as the 2 isomers SYN50810 and SYN508211), and the metabolites CSCD667584, CSCD658906, CSCD667555 (including contribution from the N-malonyl conjugate CSCD667556) and CSCD465008 using Method GRM023.03A (LC-MS/MS). The LOQ was 0.005 ppm for each sedaxane isomer and 0.01 ppm for each metabolite. Given the residue definition is sedaxane, both for enforcement and risk assessment, only the combined residues of the two sedaxane isomers, SYN508210 and SYN508211, are reported. For those samples analyzed multiple times, the mean was taken.

The residue decline data indicated that there was no accumulation of sedaxane residues in treated soybean forage, hay and seed samples.

Commodity	Total application (g a.i./100 kg seed)	n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Total Sedaxane Residues (SYN508210 + SYN508211)								
US Trials								
Soybean, Forage	40	40	<0.01	<0.065	<0.05	0.01	0.012	0.009
Soybean, Hay		40	<0.01	0.43	0.31	0.01	0.027	0.071
Soybean, Seed		40	<0.01	<0.01	<0.01	<0.01	<0.01	0

CROP FIELD TRIALS ON WHEAT

PMRA#1897942, 1897947 and 1897335

A sufficient number of trials were conducted in NAFTA representative Regions in order to evaluate the magnitude of sedaxane residues in/on wheat.

US Trials

A flowable concentrate formulation of sedaxane (SYN524464 FS) was applied as a seed treatment to wheat at a target rate of 5 g a.i./100 kg seed. Prior to application of the test material, the seed received a maintenance treatment of fungicide and insecticide. Single control and duplicate treated samples of wheat forage and hay were harvested from each plot 45 days after planting (DAP), and wheat straw and grain were harvested at maturity. A residue decline study was conducted for forage, hay, grain and straw at two trial sites.

Canadian Trials

Wheat seeds were treated with sedaxane (500FS) at a target rate of 5 g a.i./100 kg seed. Single control and duplicate treated samples of wheat forage were collected at growth stages BBCH 22-41 (31-50 DAP). Samples of wheat hay were collected at BBCH 61-85 (51-86 DAP), and wheat straw and grain samples were collected at normal commercial harvest (BBCH 89-99; 97-130 DAP). A residue decline study was conducted for forage, hay, grain and straw at two trial sites.

Side-by-side field trials were also conducted in Canada for sedaxane in/on wheat (target 5-5.2 g a.i./100 kg seed) when used as a seed treatment combination product with two other currently registered active ingredients (sedaxane/ difenoconazole/metalaxyl-M FS formulation) or three other currently registered active ingredients (sedaxane/difenoconazole/metalaxyl-M/thiamethoxam FS formulation). Residues of sedaxane were determined in wheat forage and grain.

For all the trials conducted in the US and Canada, wheat samples were analyzed for residues of sedaxane (as the 2 isomers SYN50810 and SYN508211), and the metabolites CSCD667584, CSCD658906, CSCD667555 (including contribution from the N-malonyl conjugate CSCD667556) and CSCD465008 using Method GRM023.03A (LC-MS/MS). The LOQ was 0.005 ppm for each sedaxane isomer and 0.01 ppm for each metabolite. Given the residue definition is sedaxane, both for enforcement and risk assessment, only the combined residues of the two sedaxane isomers, SYB508210 and SYN508211, are reported. For those samples that underwent multiple analyses, the mean was calculated.

For the residue decline trials conducted in the US, total residues of sedaxane (SYN 508210 and SYN508211) did not accumulate in wheat forage and hay; and were not detected above the LOQ in grain and straw.

For the residue decline trials conducted in Canada, residues of sedaxane (SYN508210 and SYN508211) were not detected above the LOQ in/on wheat forage, hay, grain and straw at any sampling interval.

Commodity	Total application (g a.i./100 kg seed)	n	Min.	Max.	HAFT	Median (STMdR)	Mean (STMR)	Std. Dev.
Total Sedaxane Residues (SYN508210 + SYN508211)								
US Trials								
Wheat, Forage	5	40	<0.01	<0.015	<0.015	0.01	0.011	0.001
Wheat, Hay		40	<0.01	<0.065	<0.045	0.01	0.017	0.012
Wheat, Straw		40	<0.01	<0.01	<0.01	<0.01	<0.01	0
Wheat, Grain		40	<0.01	<0.01	<0.01	<0.01	<0.01	0
Canadian Trials								
Wheat, Forage	5-5.2	44	<0.01	<0.01	<0.01	<0.01	<0.01	0
Wheat, Hay		32	<0.01	<0.01	<0.01	<0.01	<0.01	0
Wheat, Straw		32	<0.01	<0.01	<0.01	<0.01	<0.01	0
Wheat, Grain		44	<0.01	<0.01	<0.01	<0.01	<0.01	0

CROP FIELD TRIALS- OATS, RYE, TRITICALE

No residue data were submitted for crop field conducted with sedaxane on the small grains oats, rye and triticale. However, given that residues of sedaxane were not quantified in the grain and were low in the associated feed commodities from the wheat crop field trials, and that the TRRs were low in the grain from the corn metabolism study, the crop field trial residue data for sedaxane on wheat can be extended to oats, rye and triticale.

FIELD ACCUMULATION IN ROTATIONAL CROPS- **Spinach, radish and wheat**	**PMRA # 1897977**

A limited field rotational crop study consisting of two trials was conducted in two NAFTA growing regions.

During these trials, bare ground was treated once with a flowable concentrate formulation of sedaxane (SYN524464) and incorporated into the soil at two applications rates: 8.40-9.07 g a.i./ha and 30.6-31.6 g a.i./ha. At each site, three rotational crops (spinach, radish and wheat) were planted at 60-72, 123-132, or 266-274 day plantback intervals (PBIs) in plots treated at the two rates. Spinach leaves, radishes (roots and tops), and wheat (forage, hay, straw, and grain) were harvested at typical agricultural intervals. Control crops were planted and harvested concurrently in non-treated plots.

Spinach, radish and wheat samples were analyzed for residues of sedaxane (as the 2 isomers SYN508210 and SYN50821), and the metabolites CSCD659089, CSCD668403, CSCD465008, CSCD659087 and CSAA798670 using the LC-MS/MS analytical methods GRM023.03A and GRM023.11A. The LOQ, defined as the lowest level of method validation (LLMV), was 0.005 ppm each for SYN508210 and SYN508211, and 0.01 ppm for each of the five metabolites.

Results from this study indicate that residues of each sedaxane isomer (determined as SYN508210 and SYN508211), and the five metabolites were all below the method LOQ/LLMV (<0.005 ppm for each of the sedaxane isomers and <0.01 ppm for each of five metabolites) in/on spinach, radish, and wheat commodities at all PBIs of ~60, 120, and 270 days after application.

PROCESSED FOOD AND FEED- SPRING BARLEY	**PMRA # 1897973**
Test Site	Derbyshire, United Kingdom
Treatment	Seed treatment
Rate	40 g a.i./100 kg seeds (target)
End-use product	100FS formulation (A14635B)
Pre-harvest interval	Barley grain was collected at normal commercial harvest (BBCH 89).

Residues of the two sedaxane isomers (SYN508210 and SYN508211), and metabolites (CSCD667584, CSCD658906, CSCD659089, CSCD668403, CSCD667555- including contribution from the N-malonyl conjugate CSCD557556, CSCC210616, and CSCD465008) were each below the LOQ (<0.005 ppm for isomers and <0.01 ppm for each metabolite) in/on all samples of barley grain, and the processed fractions cleaned grain, offal, abrasion dust, pot barley, bran and flour. Therefore, processing factors could not be determined.	
PROCESSED FOOD AND FEED- BARLEY	**PMRA # 1897954**
Test Site	Northwood and Carrington, North Dakota
Treatment	Seed Treatment
Rate	15 g a.i./100 kg seed (target)
End-use product	Flowable concentrate (SYN524464 FS)
Pre-harvest interval	Barley grain was harvested at normal maturity.
Residues of the two sedaxane isomers (SYN508210 and SYN508211), and metabolites (CSCD667584, CSCD658906, CSCD667555- including contribution from the N-malonyl conjugate CSCD557556 and CSCD465008) were each below the LOQ (<0.005 ppm for isomers and <0.01 ppm for each metabolite) in/on the processed fractions pearled barely, flour and bran. Therefore, processing factors could not be determined.	
PROCESSED FOOD AND FEED- CANOLA	**PMRA#1897960**
Test Site	Carrington and Adrian, North Dakota
Treatment	Seed Treatment
Rate	22.5 g a.i./100 kg seeds (target)
End-use product	Flowable concentrate (SYN524464 FS)
Pre-harvest interval	Canola seed were harvested at maturity, 100-109 DAP.
Residues of the two sedaxane isomers (SYN508210 and SYN508211) and metabolites (CSCD667584, CSCD6568906, CSCD667555- including contribution from the N-malonyl conjugate CSCD557556, and CSCD465008) were each below the LOQ (<0.005 ppm for isomers and <0.01 ppm for each metabolite) in/on all samples of canola seed, meal, and refined oil. Therefore, processing factors could not be determined.	
PROCESSED FOOD AND FEED- CANOLA	**PMRA#1897968**
Test Site	Spruce View, Alberta and Rosthem, Saskatchewan
Treatment	Seed treatment
Rate	15 g a.i./100 kg seed (target)
End-use product	Flowable concentrate (A16148C)
Pre-harvest interval	Canola seed were collected at normal commercial harvest.
The processing study was not completed since residues of the two sedaxane isomers (SYN508210 and SYN508211) and metabolites (CSCD667584, CSCD658906, CSCD667555- including contribution from the N-malonyl conjugate CSCD557556, and CSCD465008) were each below the LOQ (<0.005 ppm for isomers and <0.01 ppm for each metabolite) in/on all samples of canola seed following a seed treatment application of sedaxane at an exaggerated rate. Therefore, processing factors could not be determined.	
PROCESSED FOOD AND FEED- SOYBEAN	**PMRA#1897964**
Test Site	Northwood, North Dakota and Sycamore, Georgia
Treatment	Seed treatment
Rate	120 g a.i./100 kg seed (target)
End-use product	Flowable concentrate (SYN24464 FS)
Pre-harvest interval	Soybean seed was collected at maturity.
Residues of the two sedaxane isomers (SYN508210 and SYN508211) and metabolites (CSCD667584, CSCD6568906, CSCD667555- including contribution from the N-malonyl conjugate CSCD557556, and CSCD465008) were each below the LOQ (<0.005 ppm for isomers and <0.01 ppm for each metabolite) in/on all samples of soybean seed, meal, hulls and refined oil, except for CSCD465008 at the LOQ (0.01 ppm) in one of six subsamples of seed and in one sample each of meal and hulls. Therefore, the processing factors could not be determined.	
PROCESSED FOOD AND FEED- WHEAT	**PMRA#1897942**
Test Site	Carrington, North Dakota and Bagley, Iowa
Treatment	Seed Treatment
Rate	15 g a.i./100 kg seed (target)
End-use product	Flowable concentrate (SYN524464 FS)
Pre-harvest interval	Wheat grain was collected at normal maturity.

Residues of the two sedaxane isomers (SYN508210 and SYN508211) and metabolites (CSCD667584, CSCD6568906, CSCD667555- including contribution from the N-malonyl conjugate CSCD557556, and CSCD465008) were each below the LOQ (<0.005 ppm for isomers and <0.01 ppm for each metabolite) in/on all samples of wheat grain, flour, bran, germ, middling and shorts. Therefore, processing factors could not be determined.

LIVESTOCK FEEDING – DAIRY CATTLE	**PMRA # 1897971**

Three groups of lactating dairy cows (with 3 cows/group) were dosed orally with capsules containing sedaxane at three target doses equivalent to 0.1, 0.5 and 2 ppm in the diet (on a dry-weight basis) for 28 consecutive days. In addition, two control cows were dosed with blank gel capsules containing no sedaxane. The actual dose rates in the feed were 0.11, 0.54 and 2.15 ppm.

The cows were milked twice daily, and milk samples were composited daily for each cow. Samples of milk from study days -1, 1, 2, 3, 5, 7, 10, 14, 17, 21, 24, and 28 from all dose groups were taken for analysis. In addition, milk collected from one high dose animal on days 1, 3, 7, 14, 21, and 28 was also separated into cream and skimmed milk samples. Animals were sacrificed ~22-24 hours after the final dose on Study Day 28. Samples of liver, kidney, fat (mesenterial, perirenal, and subcutaneous) and muscle (round and loin) were collected from each cow.

Milk and tissue samples were analyzed for residues of the two sedaxane isomers (SYN508210 and SYN508211), and the para-phenol metabolite (CSCD658906) and the para-phenol-desmethyl metabolite (CSCD659087) using Analytical Method GRM023.10A (LC-MS/MS). The LOQs for all matrices are 0.005 ppm each for SYN508210 and SYN508211 (0.01 ppm total), and 0.01 ppm each for CSCD658906 and CSCD659087.

Residues of SYN508210, SYN508211, and CSCD659087 were below the LOQ in kidney and liver samples from all three doses. However, while residues of CSCD658906 were also below the LOQ (<0.01 ppm) in liver and kidney samples from the low and mid dose groups, they were somewhat above the LOQ in two of the three liver samples (0.0101-0.0273 ppm) and two of the three kidney samples (0.0121-0.0175 ppm) from the high dose group. Muscle and fat samples were analyzed from the high dose group only. These analyses indicated that residues of SYN508210, SYN508211, CSCD658906 and CSCD659087 were all below the respective LOQs in muscle and fat.

The estimated dietary burdens are 0.02 ppm for beef cattle, 0.14 ppm for dairy cattle and 0.01 ppm for swine. These are considered to be conservative estimates of the potential exposure to residues of sedaxane given that the US soybean field trials were conducted at exaggerated rates. Based on these residue data in dairy cattle commodities, finite residues of sedaxane are not anticipated in the meat, meat byproducts and milk of cattle from the approved uses of sedaxane.

LIVESTOCK FEEDING – LAYING HENS

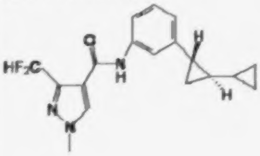
A poultry feeding study with sedaxane was not submitted. During the hen metabolism study, animals were dosed with sedaxane at ~ 18.1-23.4 ppm in the diet. This dosage used corresponds to 1.8-2.3 × 10^3 the estimated dietary burden in poultry (i.e., 0.01 ppm). Finite residues of sedaxane are therefore not anticipated in the fat, meat, meat byproducts and eggs of poultry from the approved uses of sedaxane.

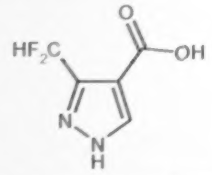
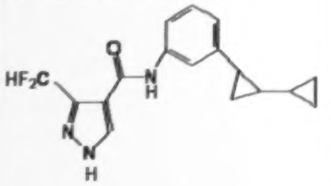
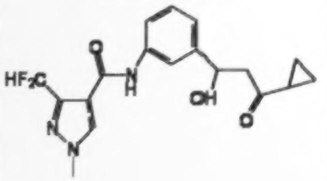
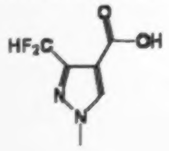
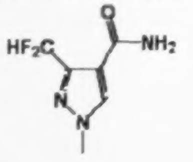
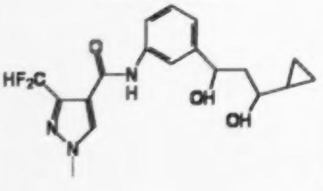
Table 6 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

<table>
<tr><th colspan="4">PLANT STUDIES</th></tr>
<tr><td colspan="2">RESIDUE DEFINITION FOR ENFORCEMENT
Primary crops
Rotational crops</td><td colspan="2">Sedaxane</td></tr>
<tr><td colspan="2">RESIDUE DEFINITION FOR RISK ASSESSMENT
Primary crops
Rotational crops</td><td colspan="2">Sedaxane</td></tr>
<tr><td colspan="2">METABOLIC PROFILE IN DIVERSE CROPS</td><td colspan="2">The metabolism of sedaxane was similar in soybean, wheat and Swiss chard.</td></tr>
<tr><th colspan="4">ANIMAL STUDIES</th></tr>
<tr><td colspan="2">ANIMALS</td><td colspan="2">Ruminant</td></tr>
<tr><td colspan="2">RESIDUE DEFINITION FOR ENFORCEMENT</td><td colspan="2">Sedaxane</td></tr>
<tr><td colspan="2">RESIDUE DEFINITION FOR RISK ASSESSMENT</td><td colspan="2">Sedaxane</td></tr>
<tr><td colspan="2">METABOLIC PROFILE IN ANIMALS
(goat, hen, rat)</td><td colspan="2">Yes</td></tr>
<tr><td colspan="2">FAT SOLUBLE RESIDUE</td><td colspan="2">Yes, based on the log K_{ow} of 3.3. However, the TRRs did not concentrate in the fat samples analyzed from the goat and hen metabolism studies.</td></tr>
<tr><th colspan="4">DIETARY RISK FROM FOOD AND WATER</th></tr>
<tr><td rowspan="11">Basic chronic non-cancer dietary risk
ADI = 0.06 mg/kg bw/day
Estimated chronic drinking water concentration = 1.9 µg a.i./L</td><th rowspan="2">POPULATION</th><th colspan="2">ESTIMATED RISK
% of ACCEPTABLE DAILY INTAKE (ADI)</th></tr>
<tr><th>Food Only</th><th>Food and Water</th></tr>
<tr><td>All infants < 1 year</td><td>0.3</td><td>0.5</td></tr>
<tr><td>Children 1–2 years</td><td>0.8</td><td>0.9</td></tr>
<tr><td>Children 3 to 5 years</td><td>0.6</td><td>0.7</td></tr>
<tr><td>Children 6–12 years</td><td>0.3</td><td>0.4</td></tr>
<tr><td>Youth 13–19 years</td><td>0.2</td><td>0.2</td></tr>
<tr><td>Adults 20–49 years</td><td>0.1</td><td>0.2</td></tr>
<tr><td>Adults 50+ years</td><td>0.1</td><td>0.2</td></tr>
<tr><td>Females 13-49 years</td><td>0.1</td><td>0.2</td></tr>
<tr><td>Total population</td><td>0.2</td><td>0.3</td></tr>
</table>

	POPULATION	**ESTIMATED RISK % of ACUTE REFERENCE DOSE (ARfD)**	
		Food Only	**Food and Water**
Basic acute dietary exposure analysis, 95th percentile **ARfD = 0.3 mg/kg bw** **Estimated acute drinking water concentration = 1.9 μg a.i./L**	**All infants < 1 year**	0.19	0.26
	Children 1–2 years	0.35	0.37
	Children 3 to 5 years	0.22	0.25
	Children 6–12 years	0.15	0.16
	Youth 13–19 years	0.08	0.10
	Adults 20–49 years	0.06	0.08
	Adults 50+ years	0.05	0.06
	Females 13-49 years	0.06	0.07
	Total population	0.12	0.14
Basic Cancer Assessment (Q_1^* = 0.00381) **Estimated acute drinking water concentration = 1.9 μg a.i./L**	**Total Population**	4.4×10^{-7}	5.9×10^{-7}

Table 7 Major Transformation Products in Environmental Media

Parent or transformation product - identity	**DT_{50}s and/or maximum % AR Soil**	**DT_{50}s and or maximum % AR Water**	**DT_{50}s and or maximum % AR Sediment**
Sedaxane, trans isomer shown (SYN508210) 	**Aerobic soil:** as seed treatment, pyrazole label, DT_{50}: 71-160 days **Aerobic soil:** as seed treatment, phenyl label, DT_{50}: 58-105 days **Aerobic soil:** bare ground treatment, pyrazole label, DT_{50}: 296-377 days **Aerobic soil:** bare ground treatment, both labelsl, DT_{50}: 60- 367 days	**Direct photolysis DT_{50}:** Aquatic photolysis DT_{50}: 45.6 days at 40°N – both labels **Indirect photolysis (natural waters) DT_{50}:** 17 days at 50°N, phenyl and pyrazole labels) **Aerobic DT_{50}:** 3.3-3.6 days, **Total system DT_{50}:** >179 days **Anaerobic DT_{50}:** 14.2 – 18.5 days, **Total system DT_{50}:** 179 - >360 days	**Aerobic system** - Rapid partitioning from water to sediment: *ca* 40% applied sedaxane in water phase 7 DAT. **Sediment:** sedaxane *ca* 2% applied 0 DAT and 83-88% 70 DAT **Anaerobic** (treated seed): DT_{50}: 423 days (extrapolated)

CSCD465008 	**Aerobic soil: 32%** Aerobic soil biotrans study using 5008 as test substance yielded DT_{50}s of 40- 157 days (SFO)	Not reported, although aquatic biotransformation study reported 15 minor transformation products (max. 1% AR)	Aquatic biotransformation study reported 15 minor transformation products (max. <1% AR). No standards
CSCD667584 (SYN545722) 	**aerobic soil:** max 4.9% AR (81 DAT)	Not reported, although aquatic biotransformation study reported 15 minor transformation products (max. 1% AR)	Identified as U14, max. reported as 0.05% AR at 70 DAT, but detected at 0.04% AR at 179 DAT in aerobic water/sediment system and reached 0.3% AR at 361 DAT in anaerobic water/sediment system
CSCD728931 	**aerobic soil:** max 8.0% AR (80 DAT)		Not reported i.e. no reference standard used in analysis
CSAA798670 (SYN449410) 	**Aerobic soil: 15.4%AR** Soil photolysis: 0.8-1.8% AR	**Direct Aqueous photolysis: 12% AR max** (sterile buffer solution) **Indirect aqueous photolysis: 26% AR** (sterile natural water)	Not reported i.e. no reference standard used in analysis
CSCC210616 (SYN508272) 	**Aerobic soil:** 2.1% AR 241 DAT *unidentified minor transformation products noted in soil photolysis study	**Direct aqueous photolysis:** 1.6% AR @ 21 and 34 DAT ***Indirect aqueous photolysis:** 5.4% AR @ 28 DAT	Reference standard was reported in aerobic/anaerobic water/sediment system study. Not identified although as many as 15 minor transformation products reported.
CSCD668094 	*unidentified minor transformation products noted in soil photolysis study	**Direct Aqueous photolysis:** 5% AR max (sterile buffer solution) ***Indirect Aqueous photolysis: 15% AR** max (sterile natural water)	Not reported i.e. no reference standard used in analysis

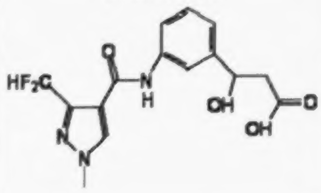
CSCD668095  HF₂C O N H OH OH O N N	*unidentified minor transformation products noted in soil photolysis study	Direct Aqueous photolysis: 6% AR max (sterile buffer solution) ***Indirect Aqueous photolysis: 16% AR max (sterile natural water)**	Not reported i.e. no reference standard used in analysis

Figure 1: Proposed Biotransformation Pathway in Soil

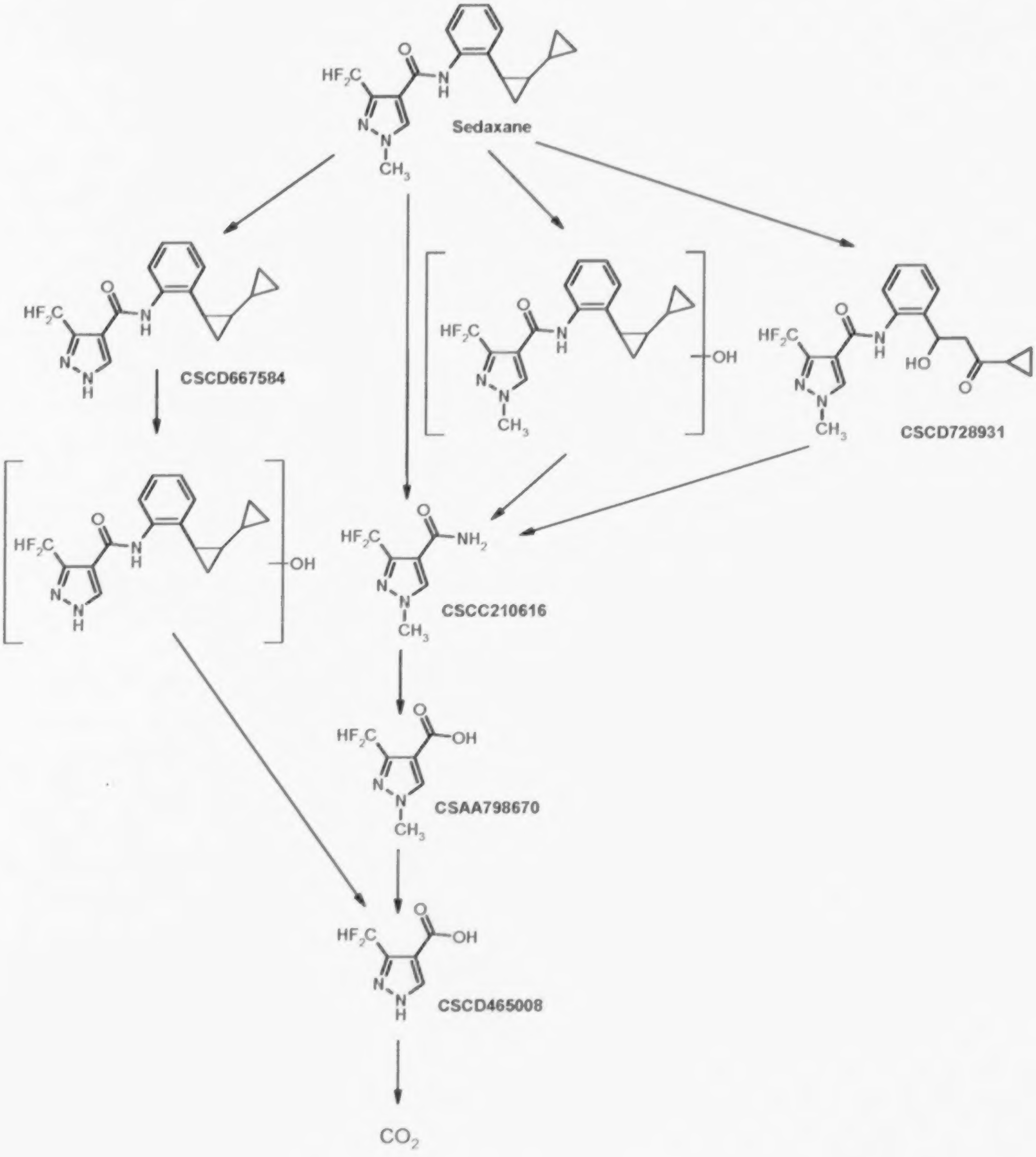

Sedaxane
CSCD667584
CSCD728931
CSCC210616
CSAA798670
CSCD465008
HF₂C
NH₂
OH
HO
CH₃
CO₂

Table 8 Fate and Behaviour in the Environment

Study	Test substance	Value	Major Transformation products	PMRA#
Abiotic transformation				
Phototransformation on soil	sedaxane	DT_{50}: 213 – 311 days		1897989 PMRA Document Number: 1897988
Phototransformation in air	sedaxane	5.1 hours (AOPWIN)		1897990
Biotransformation				
Biotransformation in aerobic soil	sedaxane	DT_{50}: 60 – 367 days DT_{90}: not observed	CSCD465008 CSAA798670	
Biotransformation in aerobic soil	CSCD465008	DT_{50}: 40-157 days DT_{90}: not observed		1897992
Biotransformation in anaerobic soil	sedaxane treated seed	DT_{50}: 375 days DT_{90}: not observed		1897987
Mobility				
Adsorption / desorption in soil	sedaxane	ads: 2.96 – 22.56 L/kg des: 4.60 – 34.15 L/kg	very highly mobile	1898007
Adsorption / desorption in soil	CSCD465008	ads: 0.02-0.10 L/kg des: 0.06 – 0.10 L/kg	very highly mobile	1898009
Soil leaching	sedaxane	conducted using tropical soils, results not relevant to Canada		1898010
Volatilization	sedaxane	v.p. = 6.5×10^{-8} Pa Henry's Law constant: 6.318×10^{9}		1897765
Field studies				
Field dissipation	sedaxane	DT_{50}: 119 – 131 days DT_{90}: 436 – 440 days		1898002 1897998
Long term (5 year) Soil Accumulation Study	A14635B (100 FS) applied as treated seed	Year 1: max. residues - 0.073 mg/kg, 127 DAT Year 2: max. residues – 0.0008 mg/kg, 112 DAT	Year 1: all transformation products <LOQ CSCD798670: Year 2, 112 DAT, 0.0025 mg/kg	1898006

Study	Test substance	Value	Major Transformation products	PMRA#
Study type	**Test material**	**Value**	**Major Transformation products**	**PMRA#**
Abiotic transformation				
Hydrolysis		stable (>365 days)	none	1898011
Phototransformation in water	sedaxane	Direct: DT_{50} = 45.6 days adjusted for dark control, 12-hour/day photoperiod, 40 °N latitude Indirect: DT_{50} – 16.5 days adjusted for dark control, 12-hour/day photoperiod, 40 °N latitude	CSAA798670 CSCD668095 CSCD668094	1898012
Biotransformation				
Biotransformation in aerobic water systems	sedaxane	867 – 950 days	none	1898014
Biotransformation in anaerobic water systems	sedaxane	1945 – 4909 days	none	1898014

Table 9 Risks to Terrestrial Organisms (Screening Level Assessment)

Organism	Exposure	Endpoint value	Uncertainty factor applied[1]	EEC	RQ[a]	LOC Exceeded
Invertebrates						
Earthworm	14d-Acute	>1000 mg a.i./kg dw soil	2	0.005 mg a.i./kg soil	1.0x10^{-05}	no
Bee	48h-Oral (invalid study)	4.22 µg a.i./bee (4.73 kg a.i./ha)	1	0.0109 kg a.i./ha	2.3x10^{-03}	no oral exposure not expected
	48h-Contact	98.2 µg a.i./bee (109.98 kg a.i./ha)	1	0.0109 kg a.i./ha	9.9x10^{-05}	no contact exposure not expected
Predatory arthropod	48h-Contact	24.6 mL EP/ha (12.3 g a.i./ha)	1	5.0E-06 g a.i./kg soil	4.1x10^{-07}	no
Parasitic arthropod	7d-Contact	320 mL EP/ha (160 g a.i./ha)	1	5.0E-06 g a.i./kg soil	3.1x10^{-08}	no
Predatory arthropod	Reproductive	NOEC <0.000060 g a.i./kg soil dw	1	5.0E-06 g a.i./kg soil	8.3x10^{-02}	no

Organism	Exposure	Endpoint value	Uncertainty factor applied[1]	EEC	RQ[a]	LOC Exceeded
Rove beetle	Reproductive	LOEC (# offspring) $\geq$0.000060 g a.i./kg dry soil	n/a	5.0E-06 g a.i./kg soil	8.3×10^{-02}	no
Vascular plants						
Vascular plant	21d-Seedling emergence	EC_{25}>107 g a.i./ha	1	10.91 g a.i./ha	0.10	no

[a] Risk Quotient (RQ) = exposure/toxicity

Table 10 Risk to Birds and Mammals (Screening Level Assessment)

Generic body weight of organism (kg)	Exposure (# seeds consumed/day)	Toxicity (# seeds consumed/day required to reach toxicity endpoint)	LOC[a]
Birds			
Small bird 0.02	168	**Acute:** > 7266	< 0.02
		Dietary: > 1785	< 0.09
		Reproduction: 1797	0.09
Medium bird 0.1	657	**Acute:** > 36329	< 0.02
		Dietary: > 8924	< 0.07
		Reproduction: 8987	0.07
Large bird 1	1917	**Acute:** > 363291	< 0.005
		Dietary: > 89241	< 0.02
		Reproduction: 89873	0.02
Mammals			
Small mammal 0.015	73	**Acute:** 2.82×10^{3}	0.02
		Reproduction: 3.89×10^{3}	0.02
Medium mammal 0.035	149	**Acute:** $>6.59\times10^{3}$	0.02
		Reproduction: 9.08×10^{2}	0.16
Large mammal 1	2267	**Acute:** 2.6×10^{4}	0.09
		Reproduction: 7.59×10^{4}	0.03

[a] Level of Concern (LOC)

Table 11 Risks to Aquatic Organisms (Screening Level Assessment)

Organism	Exposure	Endpoint value	EEC	RQ[a]	Risk
Freshwater species					
Daphnia magna	48h-Acute	5.96 mg a.i./L	0.0014 mg a.i./L	2.35x10^{-04}	negligible
	21d-Chronic	0.75 mg a.i./L		1.87x10^{-03}	negligible
Rainbow trout	96h-Acute	1.0 mg a.i./L		1.40x10^{-03}	negligible
Common carp	96h-Acute	0.62 mg ai/L		2.26x10^{-03}	negligible
Fathead minnow	33d- Early life stage (Chronic)	0.165 mg ai/L		8.48x10^{-03}	negligible
Freshwater alga *(Pseudokirchneriella subcapitata)*	96h-Acute	1.6 mg a.i./L		8.75x10^{-04}	negligible
Vascular plant	7d-Dissolved	2.7 mg a.i./L		5.19x10^{-04}	negligible
Marine species					
Crustacean *Mysidopsis bahia*	96h-Acute	1.5 mg a.i./L	0.0014 mg a.i./L	9.33x10^{-04}	negligible
Mollusk *Crassostrea virginica*	96h-Acute	3.5 mg a.i./L		4.00x10^{-04}	negligible
sheepshead minnow (*Cyprinodon variegatus*)	Acute	EC$_{50}$ = 4.2 mg a.i./L		3.33x10^{-04}	negligible
Marine alga *Skeletonema costatum*	Acute	EC$_{50}$ >6.0 mg a.i./L		2.33x10^{-04}	negligible
Amphibians	Lowest acute fish endpoint used as conservative surrogate	0.62 mg ai/L/10 = 0.062 mg a.i./L	0.007 mg a.i./L (assuming 15 cm water body)	0.11	negligible

[a] Risk Quotient (RQ) = exposure/toxicity

Table 12 Toxic Substances Management Policy Considerations-Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion value		Active Ingredient Endpoints
CEPA toxic or CEPA toxic equivalent[a]	Yes		Yes
Predominantly anthropogenic[b]	Yes		Yes
Persistence[c]:	Soil	Half-life ≥ 182 days	Half-life = 367 days (aerobic soil)
	Water	Half-life ≥ 182 days	Half-life = 18.5 days (anaerobic)
	Sediment	Half-life ≥ 365 days	Half-life = 867 – 4909 days
	Air	Half-life ≥ 2 days or evidence of long range transport	Half-life or volatilisation is not an important route of dissipation and long-range atmospheric transport is unlikely to occur based on the vapour pressure (6.5×10^{-8} Pa) and Henry's Law Constant (6.318×10^{9}).
Bioaccumulation[d]	Log $K_{ow} \geq 5$		3.3
	BCF ≥ 5000		97
	BAF ≥ 5000		not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No, does not meet all TSMP Track 1 criteria.

[a] All pesticides will be considered CEPA-toxic or CEPA toxic equivalent for the purpose of initially assessing a pesticide against the TSMP criteria. Assessment of the CEPA toxicity criteria may be refined if required (i.e., all other TSMP criteria are met).

[b] The policy considers a substance "predominantly anthropogenic" if, based on expert judgement, its concentration in the environment medium is largely due to human activity, rather than to natural sources or releases.

[c] If the pesticide and/or the transformation product(s) meet one persistence criterion identified for one media (soil, water, sediment or air) than the criterion for persistence is considered to be met.

[d] Field data (for example, BAFs) are preferred over laboratory data (for example, BCFs) which, in turn, are preferred over chemical properties (for example, Log K_{ow}).

Table 13 **Fungicidal active ingredients in alternative seed treatments registered for crop diseases on the Sedaxane 500FS Fungicide, A17511B Seed Treatment and A16874F Seed Treatment Labels**

Diseases	Crops	Active Ingredients (Resistance Management Group)
seed rots	cereals (barley, oats, rye and/or wheat)	carbathiin (7)
		carbathiin (7) + thiram (M3)
		difenoconazole (3) + metalaxyl (4)
		ipconazole (3)
		metalaxyl (4) + tebuconazole (3)
		prothioconazole (3)
		tebuconazole (3)
		tebuconazole (3) + thiram (M3)
		thiram (M3) + triticonazole (3)
		triticonazole (3)
seedling blight, root rot, or damping-off caused by *Fusarium* or *Rhizoctonia*	cereals (barley, oats, rye and/or wheat)	carbathiin (7) + thiram (M3)
		difenoconazole (3) + metalaxyl (4)
		fludioxonil (12)
		metalaxyl (4) + prothioconazole (3) + tebuconazole (3)
		metalaxyl (4) + tebuconazole (3)
		prothioconazole (3)
		tebuconazole (3)
		tebuconazole (3) + thiram (M3)
		thiram (M3) + triticonazole (3)
		triticonazole (3)
seedling blight, root rot, or damping-off caused by *Fusarium*	cereals (barley, oats, rye and/or wheat)	carbathiin (7) + thiram (M3)
		difenoconazole (3) + metalaxyl (4)
		metalaxyl (4) + prothioconazole (3) + tebuconazole (3)
		metalaxyl (4) + tebuconazole (3)
		tebuconazole (3) + thiram (M3)
		thiram (M3) + triticonazole (3)
seed decay, seedling blight or damping-off caused by *Rhizoctonia*	soybean	azoxystrobin (11)
		captan (M4)
		carbathiin (7) + thiram (M3)
		fludioxonil (12)
		fludioxonil (12) + metalaxyl (4)
		metalaxyl (4)
		metalaxyl (4) + trifloxystrobin (11)
		thiram (M3)

Diseases	Crops	Active Ingredients (Resistance Management Group)
seed decay, seedling blight or damping-off caused by *Rhizoctonia*	canola	azoxystrobin (11)
		Bacillus subtilis, MBI 600 (44)
		carbathiin (7) + metalaxyl (4) + thiram (M3)
		carbathiin (7) + metalaxyl (4) + trifloxystrobin (11)
		carbathiin (7) + thiram (M3)
		difenoconazole (3) + fludioxonil (12) + metalaxyl (4)
		fludioxonil (12)
		iprodione (2) + thiram (M3)
		trifloxystrobin (11)
seed-borne septoria	barley, rye, winter wheat	carbathiin (7) + thiram (M3)
		difenoconazole (3) + metalaxyl (4)
		metalaxyl (4) + tebuconazole (3)
		tebuconazole (3) + thiram (M3)
covered smut	barley, oats	carbathiin (7)
		carbathiin (7) + thiram (M3)
		difenoconazole (3) + metalaxyl (4)
		ipconazole (3)
		mancozeb (M3)
		maneb (M3)
		metalaxyl (4) + prothioconazole (3) + tebuconazole (3)
		metalaxyl (4) + tebuconazole (3)
		prothioconazole (3)
		tebuconazole (3)
		tebuconazole (3) + thiram (M3)
		thiram (M3) + triticonazole (3)
		triadimenol (3)
		triticonazole (3)
false loose smut	barley	carbathiin (7)
		carbathiin (7) + thiram (M3)
		difenoconazole (3) + metalaxyl (4)
		ipconazole (3)
		mancozeb (M3)
		maneb (M3)
		metalaxyl (4) + prothioconazole (3) + tebuconazole (3)
		prothioconazole (3)
		tebuconazole (3)
		tebuconazole (3) + thiram (M3)
		thiram (M3) + triticonazole (3)
		triadimenol (3)
		triticonazole (3)

Diseases	Crops	Active Ingredients (Resistance Management Group)
true loose smut	barley, oats, rye and/or wheat	carbathiin (7)
		carbathiin (7) + thiram (M3)
		difenoconazole (3) + metalaxyl (4)
		ipconazole (3)
		metalaxyl (4) + prothioconazole (3) + tebuconazole (3)
		metalaxyl (4) + tebuconazole (3)
		prothioconazole (3)
		tebuconazole (3)
		tebuconazole (3) + thiram (M3)
		triadimenol (3)
		triticonazole (3)
common root rot	barley, oats, rye and/or wheat	carbathiin (7)
		carbathiin (7) + thiram (M3)
		difenoconazole (3) + metalaxyl (4)
		ipconazole (3)
		maneb (M3)
		metalaxyl (4) + prothioconazole (3) + tebuconazole (3)
		metalaxyl (4) + tebuconazole (3)
		prothioconazole (3)
		tebuconazole (3)
		tebuconazole (3) + thiram (M3)
		thiram (M3) + triticonazole (3)
		triadimenol (3)
		triticonazole (3)
fusarium crown and foot rot	barley, rye, triticale, winter and spring wheat	difenoconazole (3) + metalaxyl (4)
		ipconazole (3)
		metalaxyl (4) + prothioconazole (3) + tebuconazole (3)
		metalaxyl (4) + tebuconazole (3)
		prothioconazole (3)
		tebuconazole (3)
		tebuconazole (3) + thiram (M3)
		thiram (M3) + triticonazole (3)
		triticonazole (3)
take-all	barley, rye, triticale, winter and spring wheat	difenoconazole (3) + metalaxyl (4)
		triadimenol (3)

Diseases	Crops	Active Ingredients (Resistance Management Group)
common bunt	rye, winter and spring wheat	carbathiin (7)
		carbathiin (7) + thiram (M3)
		difenoconazole (3) + metalaxyl (4)
		maneb (M3)
		metalaxyl (4) + prothioconazole (3) + tebuconazole (3)
		metalaxyl (4) + tebuconazole (3)
		prothioconazole (3)
		tebuconazole (3)
		tebuconazole (3) + thiram (M3)
		thiram (M3) + triticonazole (3)
		triticonazole (3)
dwarf bunt	rye and winter wheat	carbathiin (7) + thiram (M3)
		difenoconazole (3) + metalaxyl (4)
		mancozeb (M3)
		triadimenol (3)
septoria leaf blotch	winter wheat	difenoconazole (3) + metalaxyl (4)

Table 14 **Use (label) claims for A16874F Seed Treatment and A17511B Seed Treatment proposed by applicant and whether acceptable or unsupported**

Proposed use claim	Supported Use
To control general seed rots on barley, oats, rye, triticale, winter wheat and spring wheat, apply A17511B Seed Treatment at a rate of 325-650 mL per 100 kg of seed or A16874F Seed Treatment at a rate of 180-360 mL per 100 kg of seed.	Supported as proposed
To control seedling blight, root rot, and damping-off caused by seed- and soil-borne *Fusarium* spp., *Rhizoctonia* spp., or *Pythium* spp. on barley, oats, rye, triticale, winter wheat and spring wheat, apply A17511B Seed Treatment at a rate of 325-650 mL per 100 kg of seed or A16874F Seed Treatment at a rate of 180-360 mL per 100 kg of seed.	
To control seed-borne septoria on barley, rye, and winter wheat, apply A17511B Seed Treatment at a rate of 650 mL per 100 kg of seed or A16874F Seed Treatment at a rate of 360 mL per 100 kg of seed.	
To control covered smut on barley and oats, apply A17511B Seed Treatment at a rate of 325-650 mL per 100 kg of seed or A16874F Seed Treatment at a rate of 180-360 mL per 100 kg of seed.	
To control false loose smut on barley, apply A17511B Seed Treatment at a rate of 325-650 mL per 100 kg of seed or A16874F Seed Treatment at a rate of 180-360 mL per 100 kg of seed.	
To control (true) loose smut on barley, oats, triticale, winter wheat and spring wheat, apply A17511B Seed Treatment at a rate of 325-650 mL per 100 kg of seed or A16874F Seed Treatment at a rate of 180-360 mL per 100 kg of seed.	

Proposed use claim	Supported Use
To suppress common root rot on barley, oats, rye, triticale, winter wheat and spring wheat, apply A17511B Seed Treatment at a rate of 325-650 mL per 100 kg of seed or A16874F Seed Treatment at a rate of 180-360 mL per 100 kg of seed.	
To suppress fusarium crown and foot rot on barley, rye, triticale, winter wheat and spring wheat, apply A17511B Seed Treatment at a rate of 325-650 mL per 100 kg of seed or A16874F Seed Treatment at a rate of 180-360 mL per 100 kg of seed.	
To suppress take-all on barley, rye, triticale, winter wheat and spring wheat, apply A17511B Seed Treatment at a rate of 325-650 mL per 100 kg of seed or A16874F Seed Treatment at a rate of 180-360 mL per 100 kg of seed.	
To control common bunt on rye, winter wheat and spring wheat, apply A17511B Seed Treatment at a rate of 325-650 mL per 100 kg of seed or A16874F Seed Treatment at a rate of 180-360 mL per 100 kg of seed.	
To control dwarf bunt on rye and winter wheat, apply A17511B Seed Treatment at a rate of 325-650 mL per 100 kg of seed or A16874F Seed Treatment at a rate of 180-360 mL per 100 kg of seed.	
To control dwarf bunt on rye and winter wheat, apply A17511B Seed Treatment at a rate of 325-650 mL per 100 kg of seed or A16874F Seed Treatment at a rate of 180-360 mL per 100 kg of seed.	
To control early season septoria leaf blotch on winter wheat, apply A17511B Seed Treatment at a rate of 650 mL per 100 kg of seed or A16874F Seed Treatment at a rate of 360 mL per 100 kg of seed.	
To control wireworm on barley, oats, rye, triticale, winter wheat and spring wheat, apply A17511B Seed Treatment at a rate of 650 mL per 100 kg of seed.	
To suppress wireworm on barley, oats, rye, triticale, winter wheat and spring wheat, apply A17511B Seed Treatment at a rate of 325 mL per 100 kg of seed.	

Table 15 **Sedaxane 500FS Fungicide use (label) claims proposed by applicant and whether acceptable or unsupported**

Proposed use claim	Supported Use
To control (true) loose smut on barley and wheat, apply Sedaxane 500FS Fungicide as a seed treatment at a rate of 5-10 mL per 100 kg seed.	Supported as proposed
To control seed decay, seedling blight and damping-off caused *Rhizoctonia solani* on barley, wheat, oats, rye, triticale, canola, and soybeans, apply Sedaxane 500FS Fungicide as a seed treatment at a rate of 5-10 mL per 100 kg seed.	

Appendix II Supplemental Maximum Residue Limit Information—International Situation and Trade Implications

MRLs may vary from one country to another for a number of reasons, including differences in pesticide use patterns and the locations of the field crop trials used to generate residue chemistry data. As per Table 1, the proposed MRLs differ from the corresponding tolerances established in the United States (tolerances listed in 40 CFR Part 180 by pesticide). In the US, residues of sedaxane in/on triticale are covered under the tolerance established for sedaxane in/on wheat grain, and tolerances are not established for sedaxane in/on any livestock commodity. Currently, Codex[1] MRLs (Codex MRLs searchable by pesticide or commodity) have not been established for sedaxane in/on any commodity.

Table 1 Comparison of Canadian MRLs, American Tolerances and Codex MRLs (where different)

Food Commodity	Canadian MRL (ppm)	American Tolerance (ppm)	Codex MRL (ppm)
Triticale	0.01	No tolerance established*	No MRL established
Fat of cattle, goats, hogs, horses, poultry and sheep	0.01	No tolerance established	No MRL established
Meat of cattle, goats, hogs, horses, poultry and sheep	0.01	No tolerance established	No MRL established
Meat byproducts of cattle, goats, hogs, horses, poultry and sheep	0.01	No tolerance established	No MRL established
Eggs	0.01	No tolerance established	No MRL established
Milk	0.01	No tolerance established	No MRL established

*Residues of sedaxane in/on triticale are covered under the tolerance established for sedaxane in/on wheat grain.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

PMRA Document Number: 1897733
Reference: 2010, SYN524464 - GJR - Document J - Confidential Information, DACO: 2.11.1, 11.2,2.11.3,2.11.4,2.12.1,2.12.2,2.13.3,2.13.4,2.16,4.2.9,4.3.8,4.4.5,4.5.8,4.8, Document J,IIA 1.10.1,IIA 1.10.2,IIA 1.11.1,IIA 1.11.2,IIA 1.12,IIA 1.8.1,IIA 1.8.2, IIA 1.9.1.1,I

PMRA Document Number: 1897765
Reference: 2010, Sedaxane - Physico-Chemical Studies of pure and technical Substance (Section 1), DACO: 2.13.2,2.14.1,2.14.10,2.14.11,2.14.12,2.14.13,2.14.14, 2.14.2, 2.14.3,2.14.4,2.14.5,2.14.6,2.14.7,2.14.8,2.14.9,2.16,8.2.3.2,8.2.3.3,8.2.3.3.2,8.2.3.3.3, IIA 2.1.1,I

PMRA Document Number: 1897766
Reference: 2009, Sedaxane tech. - Assay by liquid chromatography, DACO: 2.13.1, IIA 4.2.1

PMRA Document Number: 1897767
Reference: 2009, Sedaxane - Validation of analytical method SA-44/1, DACO: 2.13.1,IIA 4.2.1

PMRA Document Number: 2027762
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